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Iodinated Organic Compounds As Contrast Media for Radiographic Diagnoses

VI. Experimental Studies on Emulsions of Ethyl Iodophenylundecylate (Pantopaque)[1]

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IN THE COURSE OF the experimental work leading to the development of pantopaque (ethyl iodophenylundecylate), it was observed that stable aqueous emulsions could be obtained easily with the medium (1, 2). Study of these emulsions has shown that they have the property of coating and adhering to mucosa and that they seem well adapted to the visualization of certain body cavities. In experimental examinations in dogs and other laboratory animals the most promising results have been obtained in bronchography, although satisfactory delineation may be produced in a number of other types of examination.[2]

Stable emulsions of ethyl iodophenylundecylate are formed when a 50 per cent mixture by volume with water containing up to 1 per cent of a surface active agent is passed numerous times through a colloid mill or other type of homogenizer. The surface active agents studied included bile salts, various neutral soaps, and a number of synthetics. Of these, oleyl methyl taurine (Igepon T gel) was found to be the most satisfactory when dissolved in the water phase at a concentration of 0.6 per cent. On standing, the emulsion prepared with Igepon T as a surface active agent separates into a lower milky phase, containing about 70 per cent of ethyl iodophenylundecylate, and a clear upper aqueous phase. The two phases are readily redispersed on shaking, and the resulting emulsion does not settle out for some hours. The two phases are easily separated by aspiration, or the emulsion may be diluted with isotonic saline. The size of the oil droplets in the emulsion varies somewhat with the mode of preparation, but usually they are of the order of 1.5–3.5 microns. Both the 50 and the 70 per cent emulsions may be readily injected through needles and catheters of small bore.

As reported previously (2), ethyl iodophenylundecylate has a measurable toxicity in rats and mice which is consistent with the absorbability of the medium. The process of emulsification leads to an enormous increase in surface, and this in turn affects the values of the toxicity constants. The increase in surface does not

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[2] A 50 per cent emulsion is available for investigational use from Dr. H. Sidney Newcomer, E. R. Squibb & Sons, 745 Fifth Ave., New York 22, N. Y.

Fig. 1. Bronchography in dogs with 70 per cent ethyl iodophenylundecylate emulsion. A. Overfilling obtained with intratracheal injection of 10 c.c. of the emulsion in a 12-kg. dog supine. B, C, and D. Bronchial mucosography obtained with 3 c.c. of the emulsion in an 8 kg. dog in a prone position. The roentgenograms were made over a period of fifteen minutes, the first view being taken ten minutes after introduction of the medium. Note that the upper lobe is uniformly filled.

alter significantly the LD 50 in mice as obtained by intraperitoneal injection, but does influence markedly the value found in rats. The intraperitoneal LD 50 of ethyl iodophenylundecylate has been reported to be 19 grams/kg. for 24-hour kill, while that of the emulsion has been found to be of the order of 2 grams/kg. It appears, on the basis of comparative work with other species, that the rat is particularly sensitive to ethyl iodophenylundecylate. Both ethyl iodophenylundecylate and its emulsion produce the same kind of pathological changes in the liver and kidneys of rats and mice when administered at or near the lethal level.

EXPERIMENTAL STUDIES

Bronchography: The spreading and coating properties of the emulsion were studied by making bronchograms in dogs. Other laboratory animals were briefly examined as experimental subjects but were found to be unsatisfactory.

By the procedure that was finally adopted, a dog, anesthetized with nembutal, was placed in a prone position on an animal table and rotated onto its left side. The table supporting the animal was then elevated 30° at the head, and 2 to 15 c.c. of the 70 per cent emulsion were injected under direct vision down the trachea through a small rubber tube. After two or three minutes the table was returned to a horizontal position and a series of roentgenograms was taken at intervals of five to ten minutes. Usually there was little change in the bronchogram after the first exposure. The emulsion often is seen in the smaller radicles of the bronchial system on the day following the original bronchographic study. Seven to ten days later, however, the lung fields are roentgenographically clear.

Typical bronchograms obtained by this procedure, as well as one made with the dog supine, are shown in Figure 1.

Attempts to obtain good bronchograms in anesthetized dogs with lipiodol or pantopaque proved uniformly unsatisfactory. The distribution of the media was poor. Nebulization of pantopaque was even more unsatisfactory, perhaps because of the shallow respiration that accompanies nembutal anesthesia.

Among the 16 dogs used in the bronchographic study there was one death, due to pneumonic processes initiated by a contaminant which was identified as a type of *Vibreo*. There was no evidence in the other animals of any toxic effects. Lung sections taken from four of the dogs that were autopsied showed little, if any, change that could be attributed to the effects of the medium. This was particularly well demonstrated in a 40-lb. old collie that was subjected to bronchography on four occasions at intervals of two weeks each. During the period of experimentation the dog was in excellent clinical condition. When it was killed, two weeks after the last bronchogram had been obtained, the lungs appeared darker than normal, but the gross appearance and texture were not inconsistent with the age of the animal. Microscopic sections revealed no changes that could be attributed to the use of the medium.

Retrograde Pyelography and Cystography: In two experiments with dogs the peritoneum was opened, the right and left ureters were isolated, and about 2 c.c. of the 50 per cent emulsion were injected into each kidney under slight pressure. Roentgenograms (Fig. 2) taken from these experiments show that some of the medium adheres to the wall of each kidney pelvis so that there is good to fair delineation of the calices for some time after the bulk of the medium has run out of the pelves. Follow-up roentgenograms showed that some of the medium remains in the pelves for several days.

Similar experiments in cystography (Fig. 3) in dogs gave excellent delineation of the urethra and the bladder, with some adherence to the walls of the bladder for twenty-four hours after the examination had been completed. This was particularly noticeable with the male animals.

The findings on autopsy of the dogs used for retrograde pyelography and cystog-

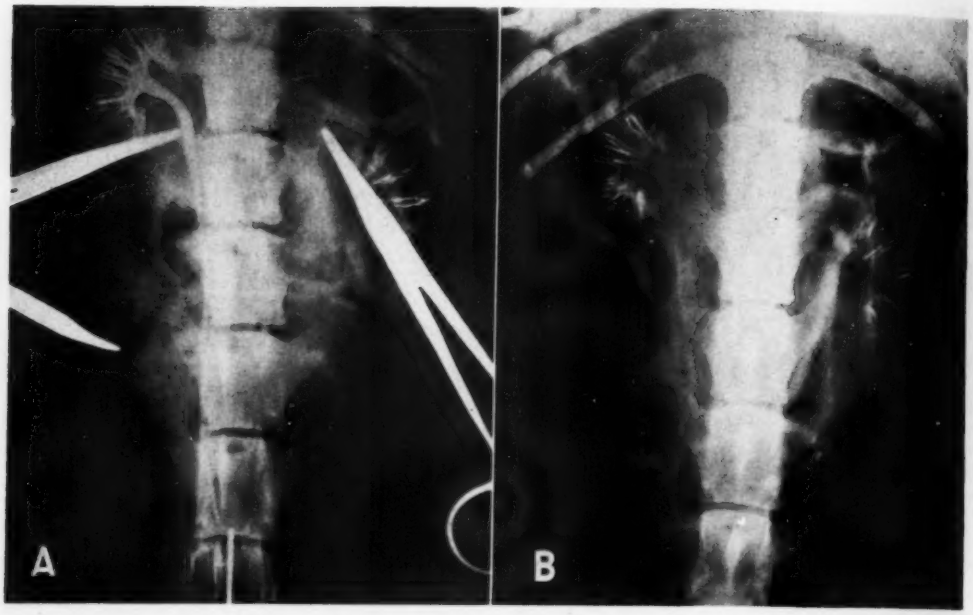

Fig. 2. Visualization with ethyl iodophenylundecylate emulsion of the renal pelves of a dog. A. Delineation obtained in the right kidney immediately and in the left kidney twenty minutes after injection. B. This film, taken thirty minutes after A, shows the residual coating on the calices after the bulk of the medium had run out.

raphy were unremarkable both grossly and microscopically.

Hysterosalpingography: The uteri of two dogs and three rabbits were exposed by laparotomies. The proximal ends of the uteri were clamped off, and an attempt was made to force the 50 per cent emulsion through the fallopian tubes. In every instance this was unsuccessful. After roentgenograms were made, the clamps were removed and the animals closed up. Subsequent roentgenograms showed that the medium remained in the uterine passages for several hours. There were no obvious disturbances in the behavior of the animals subsequently. One of the dogs was killed after eighteen days, and the other bred. The uterine passages were found to be normal in the case of the sacrificed animal, and were assumed to be functioning properly when the second dog was delivered in due course of a litter of 5 pups.

Cholangiography: Roentgenograms made following injection of the hepatic tree operatively exposed in dogs, rabbits, and rats, showed that the opacity of the 50 per cent medium was adequate for the delineation of small ducts. Two dogs were carried along after operation, and sections were made of the liver. There was no evidence of damage.

Intravenous Injections: The early preparations of the 50 per cent emulsion could not be injected intravenously with any safety, but as the technic of preparing the emulsion was improved it was found that amounts up to 1 c.c./kg. could be injected into the saphenous veins of dogs without immediate or subsequent effects. No attempt was made to determine the lethal dose, however. In rabbits, injections of 0.5 c.c./kg. in a marginal ear vein produced no early or late EKG changes.

DISCUSSION

The experimental work shows that the 50 per cent emulsion of ethyl iodophenylundecylate prepared with the aid of oleyl methyl taurine is non-toxic in the regions and at the concentrations studied. The animal experiments are not relevant as to the production of transient irritating ef-

Fig. 3. Urethrography and cystography with 4 c.c. of ethyl iodophenylundecylate emulsion in a male dog. The roentgenogram, made thirty minutes after administration, illustrates how a semi-opaque coating is retained for some time after the injection.

fects in clinical practice. There appears to be no really satisfactory method of studying this problem in animals.

One logical application of the emulsion to clinical diagnoses appears to be in relation to problems of thoracic surgery. With the current procedures, many bronchograms made with the aid of iodized oils fail to give adequate information concerning the extent and degree of disease. In recognition of this, some work is in progress to improve the results obtained with the existing media. Thus, Fariñas (3) has developed a technic for spraying iodized oils into the bronchi in order to get surface coating. To distinguish this procedure and its results from conventional bronchography, Fariñas has introduced the term "mucosography." As is evident from the illustrative bronchograms obtained with dogs through the use of the 70 per cent emulsion, the coating is of a type that reveals the details of the mucosa. It seems evident that there would be little difficulty in adapting the experimental procedure to clinical practice.

The other applications that are suggested from the animal work are not so striking, and adaptation to clinical practice may not be profitable in all fields. Nevertheless, in examinations such as cystography, urethrography, hysterosalpingography, retrograde pyelography, and cholangiography, the formation of a coating that will remain for some time may reveal additional information.

In addition to the emulsion proposed in this paper, there are a number of emulsions of iodized oils that have received study both experimentally and clinically. Emulsions prepared from water-acacia mixtures with campiodol (4) or iodochlorol have been available for retrograde pyelography for some years but have not attained

wide use. This is due in part to the fact that their viscosity is relatively high, and usually it has been necessary to inject them from a syringe rather than by a gravity method.

In 1938 a very interesting 50 per cent emulsion of ethyl triiodostearate, prepared and stabilized with the aid of lecithin and gelatin, was introduced in Germany under the name Jodsol for hepatosplenography (5, 6, 7). Since then Jodsol has been studied for angiography (8) and phlebography (9) but it is still partially in the experimental stage. Apparently the medium must be stored under refrigeration to prevent the oil particles from coalescing, and this is obviously a great disadvantage. In clinical use, up to 80 c.c. are injected intravenously, and adequate shadows of the blood vessels are obtained if the iodine concentration is 20 per cent or more.

It is uncertain whether the presently described emulsion of ethyl iodophenylundecylate is suitable for intravenous work. More experimental studies will have to be done before it can be considered for this type of application. Nevertheless, the particle size of the droplets is of the correct magnitude and the emulsion does not break down when stored for long periods of time at room temperature.

SUMMARY

Experimental studies in dogs and other laboratory animals show that emulsions of ethyl iodophenylundecylate (pantopaque) and water, prepared with the aid of 0.6 per cent of the surface active compound oleyl methyl taurine, have the property of coating and adhering to mucosal surfaces. The application of a 70 per cent medium to bronchography, and of a 50 per cent medium to a variety of other diagnostic problems, is illustrated by experimental work in dogs.

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SUMARIO

Las Emulsiones de Yodofenilundecilato de Etilo como Medios de Contraste

Los estudios experimentales en perros y otros animales de laboratorio muestran que las emulsiones de yodofenilundecilato de etilo (Pantopaco) y agua, preparadas con la ayuda de 0.6 por ciento del compuesto activo superficial, oleilo-metilo-taurina, poseen la propiedad de recubrir las superficies de las mucosas, adhiriéndose a las mismas. La aplicación de un medio de 70 por ciento a la broncografía y de un medio de 50 por ciento a otros varios problemas de diagnóstico queda demostrada por la experimentación en perros.

Iodinated Organic Compounds As Contrast Media for Radiographic Diagnoses

VII. Visualization of Empyema Cavities with the Aid of Ethyl Iodophenylundecylate Emulsion[1]

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VISUALIZATION of a group of eight empyema cavities has offered opportunities to test clinically the properties of the emulsion of ethyl iodophenylundecylate[2] described in the preceding paper (1). As brought out in that paper, the emulsion has the property of coating and adhering to tissue surfaces to a rather high degree. This has led to a more perfect delineation of the cavities and of the response of the abscesses to chemotherapy and/or surgery.

The emulsion used was one containing 50 per cent of ethyl iodophenylundecylate, corresponding to an iodine content of 15 per cent. In every instance visualization was satisfactory both fluoroscopically and roentgenographically. After injection of the medium into each cavity, it was washed out by saline lavage. Relatively small amounts of the medium were required for visualization in each instance, and the injection and lavage were carried out with a minimum of discomfort to the patient. In none of the cases was there evidence of toxic reactions of any sort.

ILLUSTRATIVE CASES

Eight empyema cavities were visualized with the aid of ethyl iodophenylundecylate emulsion. Of these, 7 were closed and 1 was open. Three of the cases are presented in some detail to illustrate the ease of use of the medium and the adequacy of the visualization.

CASE I: J. F., a 52-year-old woman, had had repeated bilateral pleural effusions for a period of eighteen years. She was subjected to numerous examinations, including lipiodol bronchography. Several years prior to this admission, the fluid in the left pleural space became infected (*Staphylococcus aureus* and anaerobic streptococcus), and a chronic empyema resulted. The cavity was drained over a period of months, during which time it was visualized three times with lipiodol. Fifteen months after a left rib resection, the cavity failed to heal spontaneously, and in order to visualize it prior to thoracoplasty, about 20 c.c. of 50 per cent ethyl iodophenylundecylate emulsion were injected (Fig. 1). Following the examination, the emulsion was washed out with saline lavage. With the patient in the prone position it was possible to inject 63 c.c. of saline into the cavity. An injection of ethyl iodophenylundecylate emulsion eleven days postoperatively showed obliteration of the cavity but demonstrated a small draining sinus. The latter was healed completely ten days after discharge.

Comparison of the visualization achieved with the emulsion of ethyl iodophenylundecylate in this case with that obtained with the iodized oil was strikingly in favor of the emulsion. Small amounts of residual oil from the early examinations had been present in the tissues for some years, and these droplets interfered with an appraisal of whether small amounts of the emulsion remained after the examination. Apparently after each examination all the emulsion was removed by the saline lavage.

CASE II: G. Q., a 64-year-old woman, had had pneumonia three times in the past. Although prior to this admission her local physician had been treating her with sulfamerazine, she was admitted

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[2] Ethyl iodophenylundecylate emulsion is available for investigational purposes from Dr. H. Sidney Newcomer, E. R. Squibb & Sons, 745 Fifth Ave., New York 22, N. Y.

Fig. 1. Case I. Visualization of a 63 c.c. open empyema cavity with 20 c.c. of ethyl iodophenylundecylate emulsion, illustrating how the medium coats all parts of the cavity.

Fig. 2. Case II. Visualization of a closed empyema cavity by injection of ethyl iodophenylundecylate emulsion. The presence of a coagulum of pus inhibits the distribution of the medium to some extent.

to the hospital because her condition was unimproved. On the day of her admission she was acutely ill and her disease continued to run an acute and toxic febrile course. At no time was a pneumococcus grown from the sputum, but *Streptococcus hemolyticus* was isolated from the fluid aspirated by thoracentesis. Treatment consisted in a combination of chemotherapy and thoracenteses. Following thoracentesis on the 33rd hospital day, ethyl iodophenylundecylate emulsion was injected through the needle into the empyema cavity to determine its size and to ascertain whether surgery was indicated at this time. On the following day a trocar was inserted and a catheter passed into the cavity. Within a few days after the catheter was inserted, the temperature returned to normal. A later visualization, on the 84th day, satisfactorily delineated a cavity much decreased in size. The patient was discharged from the hospital on her 107th day.

The visualization of the cavity on the 33rd day is shown in Figure 2. The delineation of the upper part of the cavity is inadequate, due to the use of too little medium. The patient was so acutely ill that it was inadvisable to repeat the examination with more of the contrast agent!

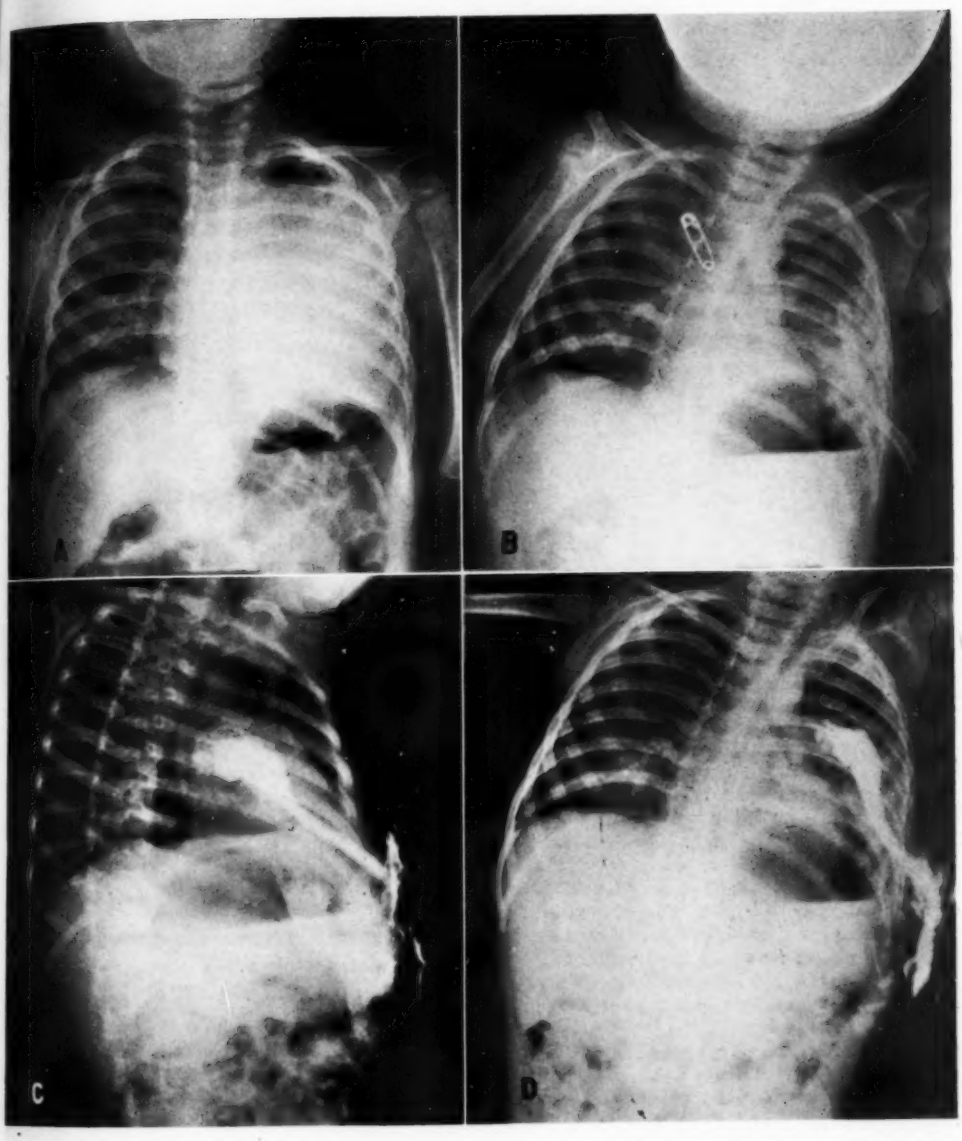

Fig. 3. Case III. Visualization of an empyema cavity by injection of ethyl iodophenylundecylate emulsion through a drainage tube. A. Condition of the chest three days after admission. B. Position of the catheter inserted on the 28th day. C and D. Visualization of the cavity following the injection of 10 c.c. of ethyl iodophenylundecylate emulsion through the catheter on the 35th day. See also Fig. 3, E and F.

The roentgenogram shows that a considerable portion of the emulsion is collected about a coagulum of pus. It is poss ble that injection of saline might have given a more uniform distribution of opacity. In subsequent procedures the ethyl iodophenylundecylate emulsion was removed by saline lavage, and at the time of discharge the chest was free of shadows due to radiopaque medium.

CASE III: E. K., a 20-month-old girl, was admitted because of abdominal pain following an upper respiratory infection of a week's duration. X-ray examination on the day of admission confirmed the

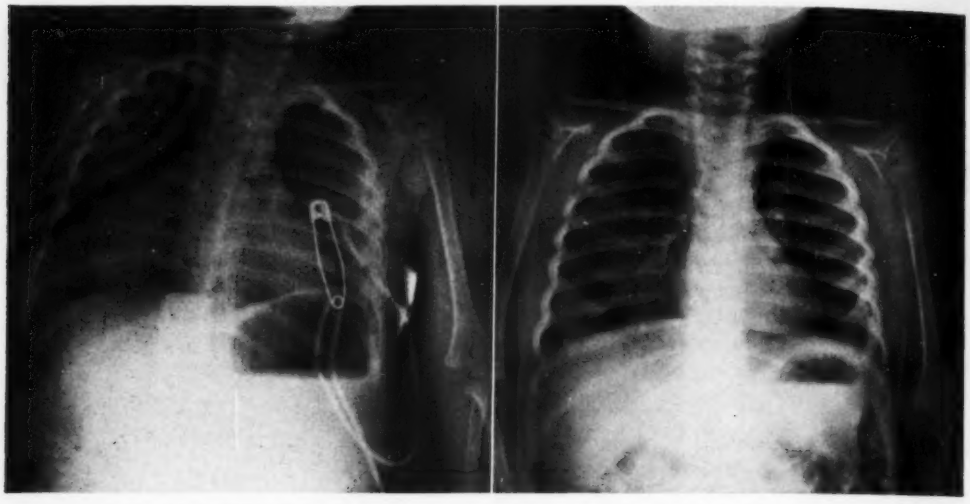

Fig. 3. E. Re-examination on the 47th day. F. Chest film 90 days after admission. The series shows the course and the progressive obliteration of an empyema cavity. The effectiveness of lavage in removing the emulsion is evident from these views.

diagnosis of bronchopneumonia in the lower lobe of the left lung, and sulfadiazine therapy was started. By the third hospital day there was clinical and roentgenographic evidence of a left hydrothorax, and culture of fluid obtained by thoracentesis yielded *Staphylococcus aureus hemolyticus*. On the fifth hospital day the thoracentesis was repeated; *Staphylococcus aureus hemolyticus* was again isolated, and administration of penicillin was started, both intrathoracically and systemically. On the 15th day of the illness a trocar was inserted to permit drainage of the cavity. Following the insertion of a larger catheter on the 28th hospital day, the patient was somewhat improved and by the 35th day was having minimal drainage from the cavity. At that time about 10 c.c. of ethyl iodophenylundecylate emulsion were introduced through the catheter to outline the cavity and to ascertain whether further surgery was required. Since only a small cavity was outlined, it was felt that there was no indication for immediate surgery, but that the patient should be followed clinically and by repeated radiopaque visualization. The catheter was left in place and chemotherapy was continued. For the next twelve days the course was relatively afebrile and asymptomatic. Examination of the cavity with ethyl iodophenylundecylate emulsion was then repeated. The cavity was found to be considerably smaller, so the patient was discharged to her home on the 55th day, and was followed in the clinic thereafter.

The course of empyema thoracis in this patient is illustrated in detail in Figure 3, to show the value of the emulsion of ethyl iodophenylundecylate in following the obliteration of the cavity, and the completeness with which the medium may be removed by saline lavage.

DISCUSSION

Through the use of the emulsion of ethyl iodophenylundecylate the visualization of empyema cavities is much simpler and more complete than by conventional methods. After introduction either directly or through a drainage tube, the medium is distributed by the normal respiratory movements to all parts of the cavity. The presence of a coagulum of pus is a handicap, however, and the medium collects to a certain degree on the surface of the coagulum. This does not appear to interfere with the delineation of the extent of the cavity and from some aspects is helpful. When the examination has been completed, the medium may be removed almost completely by saline lavage and any small residuum appears to be absorbed in a few days.

Visualization of empyema cavities is usually conducted with iodized oils. Although the procedure is essentially simple, it is often difficult to obtain good distribution of the oil, and it is frequently hard to remove it all at the end of examination. In an attempt to improve on the use of

iodized oils, Gordon (2) in 1944 employed nebulized 35 per cent diodrast or skiodan-acacia mixtures in open empyema cavities. This procedure has the advantage that after the examination all the contrast medium is absorbed, but suffers from the disadvantage that no technic has been developed for its use in closed cavities.

Since the advent of sulfa drugs and penicillin, empyema cavities are seen less frequently, and the treatment has become far more satisfactory. When a cavity does form, however, it is desirable to visualize it completely and to follow the course of corrective measures. As Blades (3) has emphasized, the cavity cannot be considered cured until it has been obliterated.

SUMMARY

The delineation of empyema cavities through the use of ethyl iodophenylundecylate emulsion has been described in detail. The medium is easily injected, distributes itself without posturing of the patient, and is readily removed by saline lavage. Where a coagulum of pus is not present, the medium distributes itself on the walls of the cavity so that double contrast studies are obtained.

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DISCUSSION

Sydney F. Thomas, M.D. (Palo Alto, Calif.): These papers are quite revealing. Mucosal studies of the trachea are something we haven't seen before and to which we are going to have to pay more attention. Mucosal studies of the urinary tract are also going to call for greater attention, because, while air contrast pyelograms have been used, they are not exactly satisfactory in the presence of non-opaque stones. This new medium should find some usefulness there.

The spreading and coating qualities of the medium are its main advantages, but another thing about it that is remarkable to me is that in one or two of Dr. Strain's cases it was completely gone at the time of the patient's discharge from the hospital. In other words, it doesn't stay in the alveoli like lipiodol and confuse one's view of the chest for months.

If anyone would raise the objection that there is a possibility of the emulsion getting into the blood vessels, Dr. Strain has already stated that they have given this material intravenously with no significant toxicity and with no electrocardiographic changes; therefore probably no embolism.

We started attacking this problem in about 1942. We did it in a little different way but were not as successful in getting a uniform emulsion with a particle size as small as Dr. Strain has produced. We had no new medium, and we used lipiodol, emulsified it, and gave it intravenously. We are interested in hepatosplenography, but there is one other use that should be mentioned—placentography. I believe we are eventually going to be able to visualize the placenta—a reticulo-endothelial organ, like the spleen and liver. There should be many other uses for this method other than those which have been mentioned here. As far as sinus tracts are concerned, I think this really is a step ahead.

William H. Strain, Ph.D. (*closing*): I shall close by supplementing my earlier remarks a bit. We have used the emulsion for cholangiograms a number of times, and have done two hysterosalpingograms with it, I believe. Dr. Golden became interested in the medium, and at his suggestion a supply was sent to Dr. C. L. Buxton at Presbyterian Hospital in New York City. There the medium was used in some eight or nine cases for the visualization of the fallopian tubes. At Presbyterian the examination is called uterotubography, an expression which I prefer. In each case Dr. Buxton reported a fair amount of reaction, but we obtained no adverse comments from the patients examined at Strong Memorial by Dr. George Heckel. In our cases the tubes were not patent, and I understand from a telephone conversation with Dr. Buxton that in all his cases the tubes were patent. Obviously the medium requires much further clinical study, and those of you who are interested may obtain some from Dr. H. S. Newcomer of E. R. Squibb & Sons.

I suspect that for some time the emulsion will be rather difficult to get. The preparation is dependent on the supply of ethyl iodophenylundecylate (pantopaque), and this in turn is dependent on the availability of undecylenic acid. As I understand the commercial situation, the supply of this acid is currently short, due to lack of adequate stocks of castor oil and the competitive use of undecylenic acid in preparations for the treatment of athlete's foot.

SUMARIO

El Yodofenilundecilato de Etilo en la Visualización de las Cavidades Empiemáticas

Mediante la inyección de una emulsión de yodofenilundecilato de etilo (véase el trabajo anterior) se obtuvo la visualizacíon roentgenoscópica y roentgenográfica de las cavidades empiemáticas. El medio se inyecta fácilmente, se esparce sin que haya que cambiar la posición del enfermo y se extrae fácilmente por medio del lavado con solución salina. Si no hay coágulo de pus presente, el medio se reparte por las paredes de la cavidad, de modo que se logran estudios de doble contraste. Tres de los 8 casos en que se utilizó el procedimiento son descritos.

Iodinated Organic Compounds
As Contrast Media for Radiographic Diagnoses

VIII. Studies on Tetraiodophthalimidoethanol as a Medium for Gastro-Intestinal Visualization[1]

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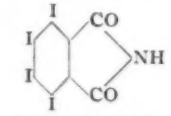
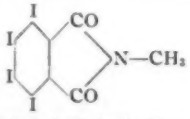
APPARENTLY NO serious attempt has been made to utilize iodinated organic compounds for the visualization of the gastro-intestinal tract. Iodized oils are used to a limited extent for specialized examinations, and there are occasional reports of experimental attempts to employ other iodinated compounds.

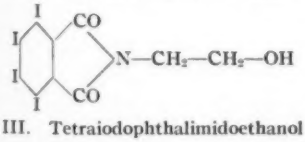
To evaluate the possibilities of particulate iodinated organic compounds for gastro-intestinal work, tetraiodophthalimide (I), tetraiodophthalimidomethane (II), and tetraiodophthalimidoethanol (III) were synthesized and studied experimentally in dogs and to a limited extent clinically. It was soon apparent that the parent compound, tetraiodophthalimide, produced increased motility of the stomach. Although this effect may be useful for certain specialized problems, it does not appear to be a desirable quality for general use. Attention was then turned to tetraiodophthalimidoethanol. After some study it was found that this medium, when ground in water to a particle size of 1 to 2 microns, formed a suspension that had a number of desirable qualities. In comparison with barium sulfate suspensions, tetraiodophthalimidoethanol suspensions do not settle out as readily, are not so gritty, delineate more completely experimentally produced gastric lesions, adhere better to the bowel wall, and apparently do not inspissate so readily.



I. Tetraiodophthalimide



II. Tetraiodophthalimidomethane



III. Tetraiodophthalimidoethanol

Tetraiodophthalimidoethanol is a light yellow solid with a slightly greenish cast. The medium contains 73 per cent iodine and is considerably more opaque to x-rays than barium sulfate. The preparation of suitable aqueous suspensions on an experimental scale is a time-consuming process, since the product of chemical synthesis must be micronized in the dry state and then ground in a ball mill with water for several weeks. A properly prepared suspension is essentially non-settling at concentrations above 15 per cent by weight and becomes very thick at concentrations above 30 per cent.

Studies on toxicity are still somewhat incomplete, but it appears that tetraiodophthalimidoethanol is of about the same order of toxicity as barium sulfate. Oral administration to fasting rats in doses up to 15 grams/kg. produced no toxic symptoms. Intraperitoneal injections in mice

[1] Accepted for publication in December 1946. Presented before the Radiological Society of North America at the Thirty-second Annual Meeting, Chicago, Ill., Dec. 1–6, 1946. This work was aided by a grant from the Research Laboratories of the Eastman Kodak Co., Rochester, N. Y.

Fig. 1. Photograph of a dog's stomach showing the site and type of marginal ulcer (arrow) produced by histamine-beeswax injections after gastrojejunostomy. In the illustration the esophagus is at the top, the afferent loop is on the left, and the efferent loop on the right.

were productive of toxic manifestations at the range of 7.5 to 10 grams/kg. In comparison, barium sulfate suspensions when injected intraperitoneally in mice produced similar but less severe reactions at the same level of 7.5 to 10 grams/kg. Growth curves of rats raised on diets containing 4 per cent of added tetraiodophthalimidoethanol were more nearly normal than those obtained with 4 per cent added barium sulfate, but this may be due entirely to the effect of particle size, since the tetraiodophthalimidoethanol averaged about 10 microns, and the barium sulfate 1 to 2 microns.

EXPERIMENTAL STUDIES

Preparation of Suspensions: Tetraiodophthalimidoethanol as obtained by synthesis consisted of needles varying in particle size from 3 to 25 microns. Suitable suspensions with a particle size of 1 to 2 microns were prepared from the stock material either by wet ball-milling with water for ten to twelve weeks or by wet ball-milling of a micronized product for two to three weeks. The ball-milling was done in a 1-gallon apparatus using charges of about 2 kg., of which usually 25 per cent was the iodinated medium. Periods of ball-milling shorter than those specified were inadequate to reduce the particle size uniformly to 1.5 to 2 microns.

Commercial barium sulfate was found to have a particle size of 1.5 to 3 microns, and to be fairly uniform in composition. By micronizing or by wet ball-milling, the size of the particles could be reduced to 1 to 2 microns, and the uniformity could be improved slightly. Suspensions were prepared either by wet grinding or by following the clinical practice of stirring barium sulfate with water mechanically. For some of the work, gelatin (1) or starch was added to give better suspensions.

Gastro-Intestinal Series in Dogs: Initially the iodinated medium was compared with barium sulfate suspensions by studying the delineation of the rugal pattern in normal dogs. Although the iodinated medium uniformly gave more satisfactory visualization of the rugae, it was felt that the experimental test was not critical enough. A much more satisfactory test object was found in dogs in which marginal stomach ulcers had been produced by the general technic developed by Code and Varco (2). In such dogs an ulcer is produced by intramuscular injections of histamine-beeswax following various types of gastrojejunostomy. The anatomical relationships that are produced are illustrated by the photograph (Fig. 1) of a stomach of one of the dogs used in the work. Comparative studies were made with barium sulfate suspensions and with tetraiodophthalimidoethanol suspensions in 4 such dogs. In 3 dogs an ulcer or stomach lesion was demonstrated with the iodinated medium, but in only one of these was the stomach lesion delineated when barium sulfate was used. In the fourth dog no lesion could be demonstrated either with the iodinated medium or with barium sulfate and none was found on autopsy. The comparison of the two media in one dog is shown in Fig. 2, in which a filling defect at the line of anasto-

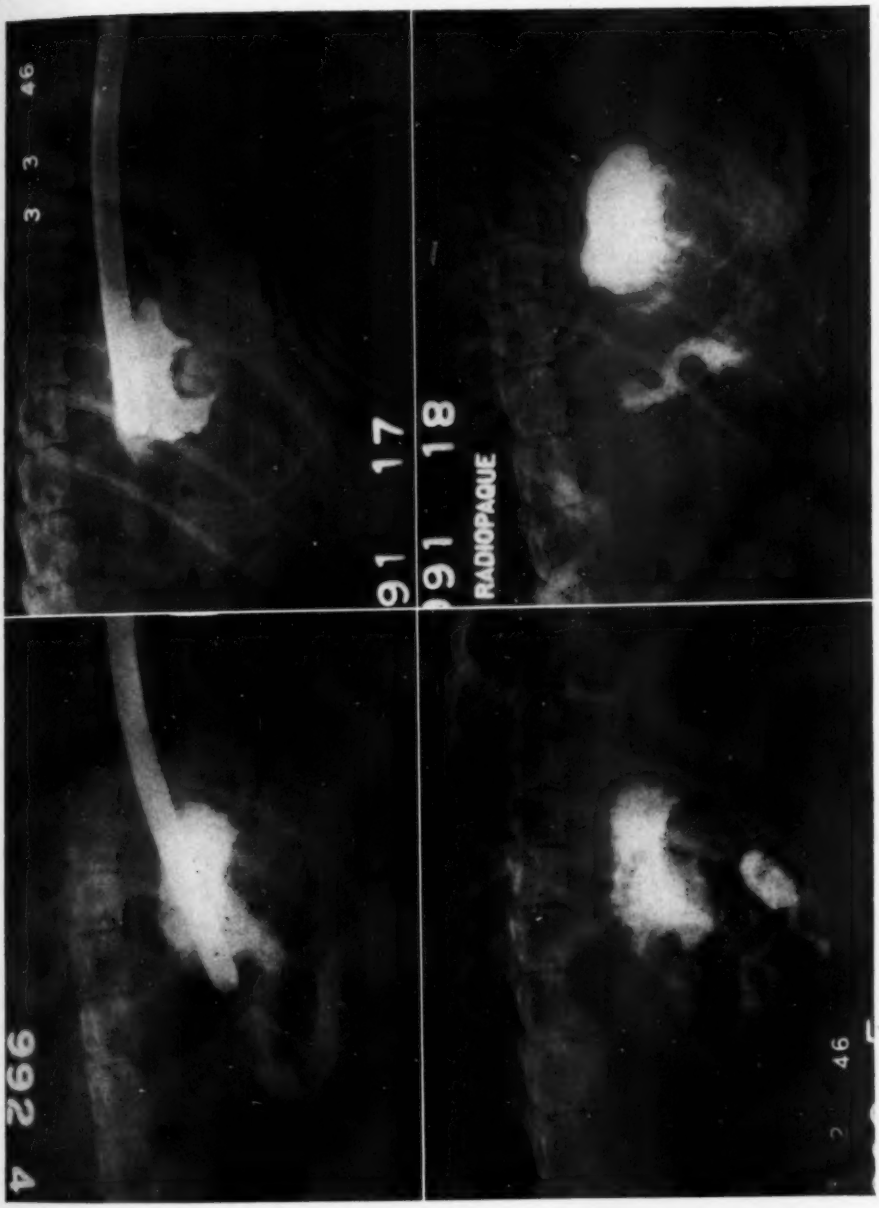


Fig. 2. Comparative visualization with barium sulfate and tetraiodophthalimidoethanol of a marginal ulcer in the stomach of a dog. A and B show the distribution of barium sulfate, A being taken immediately after administration, and B after twenty minutes. C and D show the delineation of the ulcer with tetraiodophthalimidoethanol, C being the view on administration, and D the delineation after twenty minutes.

mosis is visualized in the examination conducted with tetraiodophthalimidoethanol, but not in the one with barium sulfate.

The technic of the examination was varied somewhat with each animal. First each dog was anesthetized with nembutal

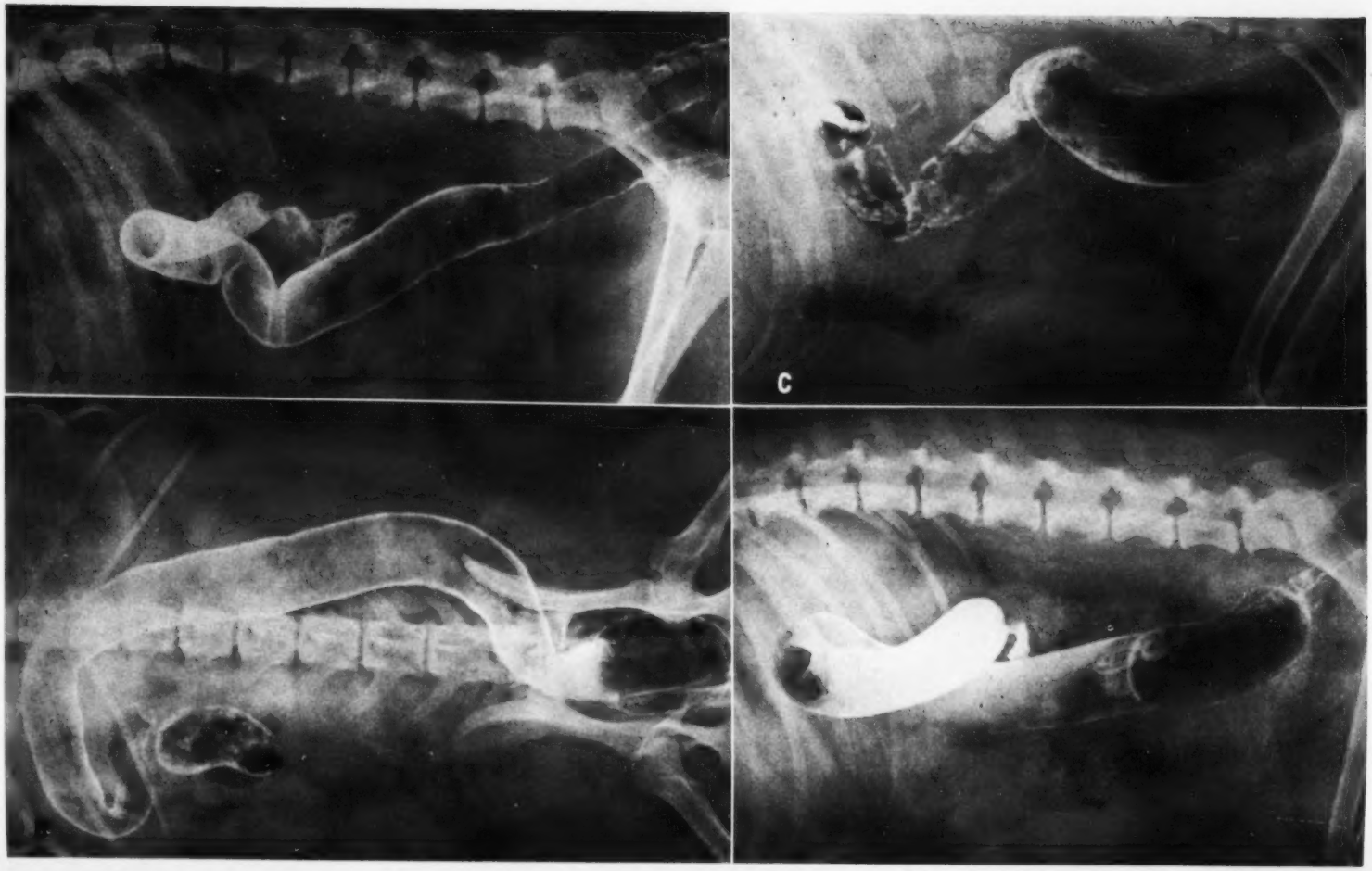


Fig. 3. Double contrast studies of the bowel of the same dog, comparing the adherence of tetraiodophthalimidoethanol and barium sulfate. A and B, made with tetraiodophthalimidoethanol, show uniform coating both in the lateral and anteroposterior views. Studies with barium sulfate are shown in C, where the coating is very poor, and D, where the medium has settled to the dependent portion of the bowel to give a fair coating.

and placed in a supine position. By means of a stomach tube, a dose of 50–70 c.c. of the suspension of the contrast medium under study was then given. A series of roentgenograms was then made at intervals during the first thirty minutes with the animal in various positions. As a variant, the dog was placed in an upright position with the hindquarters supported by a sling.[2] No one position was uniformly satisfactory, but with each dog there was usually an ideal position.

Because of the extensive alterations in the arrangement of the intestines as a result of the operative intervention, roentgenograms taken more than thirty minutes after the administration of the medium were difficult to interpret.

To study the inspissating characteristics of tetraiodophthalimidoethanol, the feces of dogs fed with the medium were compared with those given barium sulfate. Almost uniformly the consistency of the feces was much softer when the iodinated medium was used. An extended experiment was carried out with a 10-kg. dog that was to be sacrificed in connection with another problem. This animal received two doses daily of 19 grams of tetraiodophthalimidoethanol for a period of eight days. At autopsy the entire digestive tract was found to be filled with varying amounts of the yellow tetraiodophthalimidoethanol, and the consistency was found to become progressively harder as the rectum was approached. Both grossly and microscopically the tissue of the digestive tract was unremarkable.

Opaque Enemas in Dogs: The procedure for the visualization of the large bowel of the dog was varied from time to time, but the following technic is typical of the method giving the most uniform results:

The dog was anesthetized with nembutal, placed in a supine position, and given a tepid enema of isotonic saline. Usually from 3 to 5 liters of saline were necessary to clear the large intestine of all feces. About an hour after the saline enema was completed, the dog was given an enema of the radiopaque medium under consideration. Nembutal markedly relaxes the anal sphincter, and it was impossible for the dog to retain the enema without the use of a Foley catheter. Even with this device, retention was often difficult because the catheter would slip out over the smooth mucosal surface. After a waiting period of fifteen minutes, corresponding to the time involved clinically in fluoroscopy, the medium was expressed by gentle palpation of the abdomen, and the large intestine was insufflated through the Foley tube with 70 to 100 c.c. of air. Routine anteroposterior and lateral films were taken after each step in the procedure. Following the examination, the dog was rested for four to seven days before the procedure was repeated with the same or another radiopaque medium.

To appraise the adherence of each medium to the mucosal surfaces, it was necessary to take both anteroposterior and lateral films after the air insufflation. Thus the coating on all surfaces of the bowel wall could be studied (Fig. 3). The roentgenograms were then graded to evaluate the comparative excellence of the delineation of the bowel wall with the various suspensions.

For an examination to be considered "excellent," 75 per cent or more of the bowel wall in both views had to be covered with a uniform thin coating of the medium. Roughly half of the bowel had to be coated if the examination was to be rated as "good." An examination was considered "fair" if less than 50 per cent of the bowel wall was delineated. Variable results were obtained in the "poor" examinations. In most of them little if any of the mucosal surface was covered with medium, while in some series the medium had settled out of suspension onto the dependent bowel wall. Table I summarizes the 33 examinations which were done, using 6 dogs. The data on barium sulfate include the results obtained with U.S.P. barium sulfate, I-X barium sulfate, barium sulfate and starch, and barium sulfate and gelatin

Fig. 3. Double contrast studies of the bowel of the same dog, comparing the adherence of tetraiodophthalimidoethanol and barium sulfate. *A* and *B*, made with tetraiodophthalimidoethanol, show uniform coating both in the lateral and anteroposterior views. Studies with barium sulfate are shown in *C*, where the coating is very poor, and *D*, where the medium has settled to the dependent portion of the bowel to give a fair coating.

[2] The authors are indebted to Dr. Ross Golden for the suggestion that this position be employed.

TABLE I: COMPARISON OF DOUBLE CONTRAST BOWEL STUDIES

Medium	Tetraiodophthalimidoethanol				Barium Sulfate			
Results	Excellent	Good	Fair	Poor	Excellent	Good	Fair	Poor
Dog 1	2	1	..	..	..	2	2	3
2	1	..	..	..	1	..	1	1
3	..	2	..	..	..	2	..	1
4	..	1	..	1	..	1	1	3
5	1	..	..	..	..	1	..	1
6	..	1	..	1	..	..	..	2
Total	4	5	0	2	1	6	4	11
Per cent	36	46	0	18	5	27	18	50

according to the formula published by Abel (1). In passing, it may be noted that most of the modified barium sulfate formulas were less satisfactory than barium sulfate *per se*.

CLINICAL STUDIES

In all, 56 oral examinations and 4 opaque enema studies were carried out clinically with the suspensions of tetraiodophthalimidoethanol. Many of the early examinations were made with suspensions in which the particle size was of the order of 3.5 to 8 microns, and the findings were not remarkable. It became apparent from these preliminary trials that the suspensions of tetraiodophthalimidoethanol were easier to take than barium sulfate suspensions. The patients found the taste of the suspension of the iodinated medium comparable to that of milk of magnesia.

The increased palatability of suspensions of tetraiodophthalimidoethanol over barium sulfate suspensions was brought out particularly well in a student experiment that was conducted on the relative rates of passage of white and "peeled wheat" breads through the stomach. In the course of this work, measured amounts of the two kinds of bread were soaked in the suspension of either barium sulfate or of tetraiodophthalimidoethanol and ingested on an empty stomach. After a number of experiments of this type, the student group was unanimously in favor of the use of the iodinated medium. None of the students noted any effects that might be attributed to the series of weekly doses of 20 to 25 grams of tetraiodophthalimidoethanol.

Eighteen hospital cases were examined with the suspension of the iodinated organic medium. Several of these were studied, also, with the aid of barium sulfate meals. In only one instance did the examination with tetraiodophthalimidoethanol disclose a lesion that was not revealed by barium sulfate. In this case there was an area in the small intestine that was delineated by tetraiodophthalimidoethanol but not by barium sulfate; there was no opportunity to confirm this observation.

Several of the patients examined with tetraiodophthalimidoethanol were in terminal stages of disease, and in two cases it was possible to study autopsy material. In these patients there was no evidence of the medium in the intestine, nor were there any findings that could be attributed to the use of the medium.

At no time did any of the patients or student investigators find that tetraiodophthalimidoethanol was productive of undue constipation. The consistency of the feces was firmer, as would be expected as a result of adding an undigested solid organic compound, but laxatives were not required for adequate elimination. This comparison with barium sulfate is inadequate, because the retention of normal mobility is due in part to the fact that the greater opacity of the iodinated compound permitted the use of small amounts.

DISCUSSION

The first consideration for any preparation proposed for use as a contrast medium is a proper appraisal of its toxicity. Tox-

icity studies on a medium advocated for use in gastro-intestinal work should include a consideration of the response of animal tissues to the preparation in the digestive tract, in the peritoneal cavity, and in the lower respiratory tract. The studies on tetraiodophthalimidoethanol have been quite complete with respect to the digestive tract, moderately complete with regard to the peritoneal cavity, and inadequate in relation to the respiratory system. The information available from the animal studies is adequate for clinical appraisal in selected cases, however, but should be supplemented by further observations if the medium proves promising in clinical applications. Many problems are difficult to solve satisfactorily. In illustration, there may be cited the question of whether it is safe to use barium sulfate in infants, where there is the possibility that some of the medium may on occasion be aspirated into the respiratory tract. The relatively rare occurrence of barium sulfate entering the peritoneal cavity through perforation of an ulcer has raised similar questions. From a practical point of view, the damage to the system resulting from such peritoneal escape appears to be tolerable (3).

At the outset of the work, it was felt that the property of remaining in suspension was the most important aspect of a radiopaque medium designed for use in gastro-intestinal work. The many admixtures that are made with barium sulfate to accomplish this purpose naturally influenced this point of view. As the work progressed, it became apparent that adherence to the gastric mucosa was of equal, if not greater, importance, if progress were to be made in increasing the accuracy of the gastro-intestinal series or of the opaque enema study. It is quite apparent from the results of the oral administration of barium sulfate and of tetraiodophthalimidoethanol to dogs with stomach lesions that the accuracy of the delineation was much greater with the iodinated medium than with the standard barium sulfate.

With the opaque enemas the double contrast studies were uniformly better with tetraiodophthalimidoethanol than with barium sulfate. Surprisingly, the incorporation of additives with barium sulfate appeared to decrease the adherence of the medium to the bowel wall. This was not always apparent when anteroposterior views alone were taken, but became evident only when both lateral and anteroposterior exposures were made.

Although experimentally the iodinated medium is superior to barium sulfate in that it does not settle out as readily, adheres better to the bowel wall, and apparently does not inspissate as readily, it remains to be shown that these advantages make for more accurate interpretations in normal clinical practice. From the limited clinical experience that is now available, it can be said only that suspensions of tetraiodophthalimidoethanol are more palatable than barium sulfate and appear to be free of toxic reactions. Before a large scale clinical trial can be considered, it must be shown that an iodinated organic compound, one that will be relatively expensive, will give enough information to justify the cost. Work is under way to make a critical comparison clinically of such new media in selected cases.

SUMMARY

Comparative studies in dogs of barium sulfate suspensions and of tetraiodophthalimidoethanol suspensions show that the iodinated medium gives more complete and more accurate delineation of experimentally produced stomach lesions. Double contrast enema studies in dogs were similarly much more satisfactory with the iodinated organic medium than with barium sulfate. A limited clinical experience with tetraiodophthalimidoethanol has shown that the new medium is more palatable than barium sulfate, and apparently as safe to use. Further use of the new medium is dependent on the outcome of critical comparisons with barium sulfate in selected clinical cases.

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DISCUSSION

Ray Carter, M.D. (Los Angeles, Calif.): One can only discuss this paper optimistically, and perhaps wishfully, because of the well known deficiencies of our ordinary barium medium. Attempts to improve the qualities of barium have met with only moderate success, and now, when mucosal pattern studies are crucial, any potential improvement is of great interest. As a matter of fact, improvement doesn't have to be outstanding, as this appears to be at first sight. Even if it gives a reasonable improvement of our roentgenologic images, it will be well worth while.

The cost, of course, always has to be considered, but there are fallacies there. The cost of the opaque material is a minor part of the cost of an examination. Any reasonable added expense would actually be an economy if it increased the information obtained.

Thorium dioxide sol has served well in the alkaline medium of the colon, but we do not yet have a contrast substance that shows so clearly the mucosal pattern in the stomach. It will be interesting to see what mucosal pattern will be revealed in the small intestine by this new medium. Here again minute details are crucial.

Again, one can only hope this medium will prove to be safe, reasonable, economical, and thoroughly useful.

Robert R. Newell, M.D. (San Francisco, Calif.): Of course, I have no experience with this material. I have been discouraged about the shortcomings of barium, and many years ago I made some experiments with alginic acid to keep barium from settling out. They were very successful but I never had the energy to complete them. Maybe I will some day.

Various things ought to be investigated, of course, if barium seems sufficiently unsatisfactory that one could really afford to spend ten dollars a patient in order to get some other material which might be slightly better.

We have tried umbrathor, the less expensive thorium dioxide suspension, for contrast enemas; we were told that it had the advantage that it precipitated out on the mucosa. It does, but that is a disadvantage rather than an advantage, so we have returned to barium for contrast studies. I was interested to see the very high smears obtained around the inside of the colon in dogs. If this material proves to smear itself over the inside of the large intestine better than barium does, I should say that it would be very well worth using for contrast enemas, because I think that the search for polyps in the colon now leaves us with too many oversights. We could afford to spend almost any amount of time and effort to better our percentage of success in that region.

Maurice Feldman, M.D. (Baltimore, Md.): I would like to ask Dr. Strain what effect this medium has on other structures of the body, whether he has made any blood studies, and whether there is any iodine absorption, and how the drug is eliminated.

Hans Armin Jarre, M.D. (Detroit, Mich.): There is no need of repeating again the disadvantages which we have encountered with barium, but it is a pleasure to hear that some efforts are being made to obtain a better contrast medium. In that respect it might be worth while to reopen a chapter which has been given very little attention during the past.

There is one chemical at least available which is excreted by the gastric mucosa: neutral red. Some years ago I persuaded the University of Wisconsin and Dr. Pohle to experiment with neutral red, combining iodine in various forms with derivatives of this chemical, and while the results were not successful in the sense that they were practical in radiologic application, it was nevertheless possible to obtain a faint accumulation of such chemicals in the gastric mucosa and probably in the gastric glands themselves.

It is quite possible that research, as we have heard today, may be conducted along similar lines and that the possibilities of excretion of contrast material by the gastric wall may be re-investigated, so that functioning areas may be more readily differentiated from non-functioning areas—that normal areas may be differentiated from pathological areas.

William H. Strain, Ph.D. (*closing*): We don't know all the answers on the pharmacology of tetraiodophthalimidoethanol, but we do know that it is not absorbed to any extent. We have had a number of blood iodine determinations made and expect to have some further analyses carried out; to date all have been in the "physiological range." The particle size will influence somewhat the amount of absorption, and until we have decided on just the particle size we shall want to use there is no particular point in further studies.

As brought out in the paper, we have incorporated the medium in diets of rats—a sort of standard procedure with many new drug preparations—to see how it influenced the rate of growth. To our surprise, tetraiodophthalimidoethanol retarded the

growth less than barium sulfate. We think the explanation is entirely a physical one, since the barium sulfate particles were slightly smaller.

We have made some intravenous injections in experimental animals. This is a very interesting experiment because the particle size determines where the particular medium will go, and in EKG measurements there is a convenient tool for determining whether the capillaries of the lungs become plugged. We are going to do some additional work of this sort. We now have a stock of a variety of particle sizes, and we should be able to do a rather polished job on the distribution in the organs of experimental animals.

SUMARIO

El Tetrayodoftalimidoetanol como Medio Gastrointestinal

Estudios comparados de las suspensiones de sulfato de bario y de tetrayodoftalimidoetanol realizados en los perros revelan que el medio yodado facilita una delineación más completa y exacta de las lesiones producidas experimentalmente en el estómago. Los estudios con enemas de doble contraste fueron igualmente más satisfactorios con el medio orgánico yodado que con el sulfato de bario. Una limitada prueba clínica con el tetrayodoftalimidoetanol demuestra que el nuevo medio posee sabor más agradable que el sulfato de bario, y es aparentemente igualmente inocuo. El empleo ulterior del tetrayodoftalimidoetanol depende del resultado de las comparaciones analíticas con el sulfato de bario en casos clínicos.

Mucosal Deformities of the Greater Curvature of the Stomach[1]

MAURICE FELDMAN, M.D.

Baltimore, Md.

IRREGULARITIES of the greater curvature are commonly observed in the routine roentgen examination of the stomach. Normally the silhouette of the greater curvature is smooth in contour, but occasionally it will present a slightly corrugated, serrated, or cog-wheel appearance due to prominence of the mucosal folds. These serrations are usually regular and rounded in contour. In pathologic conditions of the gastric mucosa the serrations along the greater curvature become enlarged, widened, and irregular. In cases of peptic ulceration associated with gastritis the folds often become very prominent. When the gastric mucosa is greatly hypertrophied, the folds on the greater curvature appear thickened, irregular, and spiked, while the spaces between the folds are markedly widened. These enlarged gastric mucosal folds are best seen on the greater curvature; the lesser curvature usually retains its smooth contour. This is due to the horizontal arrangement of the folds on the lesser curvature, whereas the folds on the greater curvature run at right angles and are transverse or oblique.

Since the study of the gastric mucosal folds has become a routine part of the examination of the stomach, the various changes occurring in the normal and pathologic states must be properly interpreted and differentiated. Numerous diagnostic problems have been encountered following the demonstration of deformities of the greater curvature, resulting from the changes in the mucosal folds. The normal mucosal folds may be redundant and hang down from the cardia of the stomach, producing a filling defect. At times the gastric folds become tremendously enlarged and produce a filling defect on the greater curvature simulating a neoplasm.

Fig. 1, A. Case 1. Marked deformity of the greater curvature with enlargement of the mucosal folds. See Fig 1, B–E.

In this paper nine cases are reported, presenting digestive symptoms and abnormal roentgen findings of the greater curvature of the stomach which conformed to no distinct disease pattern.

CASE REPORT

CASE I: A woman aged 56 gave a six months history of weakness, weight loss of 30 pounds, vertigo, anorexia, nausea, and constipation. On physical examination she appeared undernourished, with evidence of a considerable loss of weight. The abdominal examination was negative and no mass was felt. Laboratory findings revealed a secondary anemia, normal urine, and negative Wassermann reaction. Gastric analysis showed a total acidity of 40 and free hydrochloric acid 20.

A gastro-intestinal roentgen study disclosed a large, irregular, ulcerating filling defect on the greater curvature of the stomach simulating a malignant neoplasm and unusually large hypertrophied mucosal folds. Gastroscopic examination

[1] Presented at the Thirty-second Annual Meeting of the Radiological Society of North America, Chicago, Ill., Dec. 1–6, 1946.

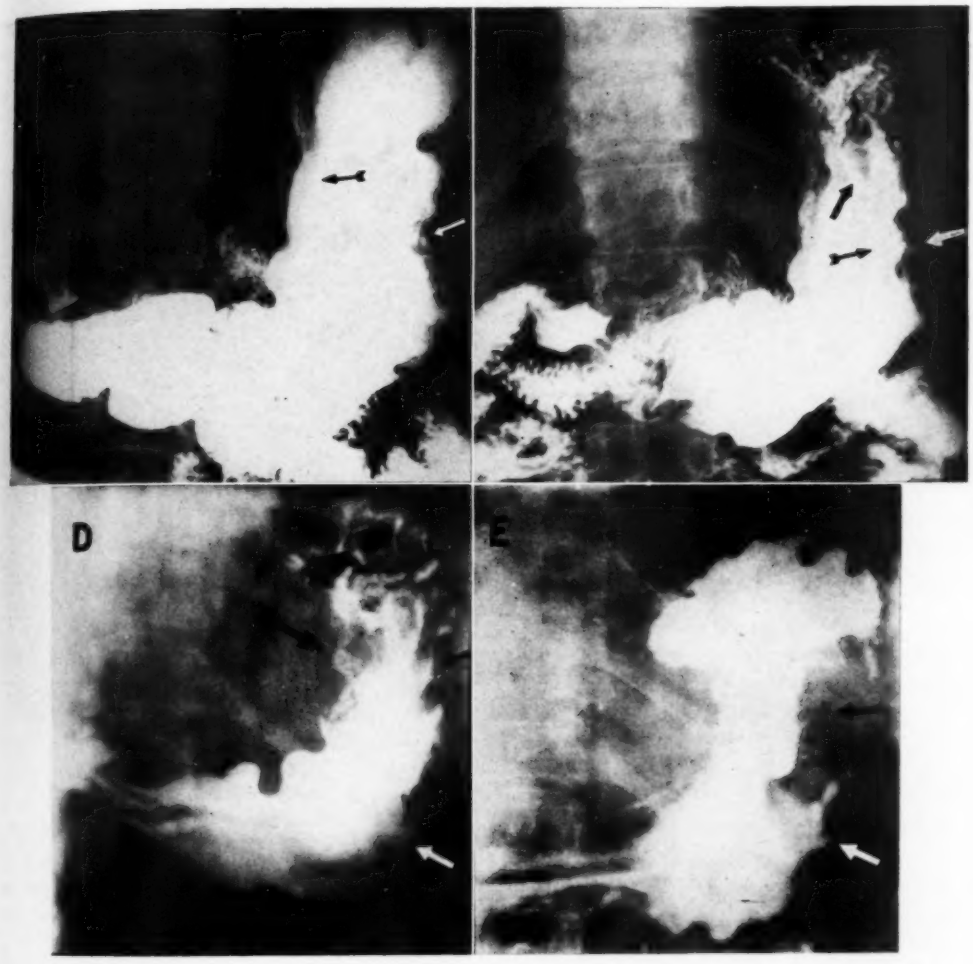
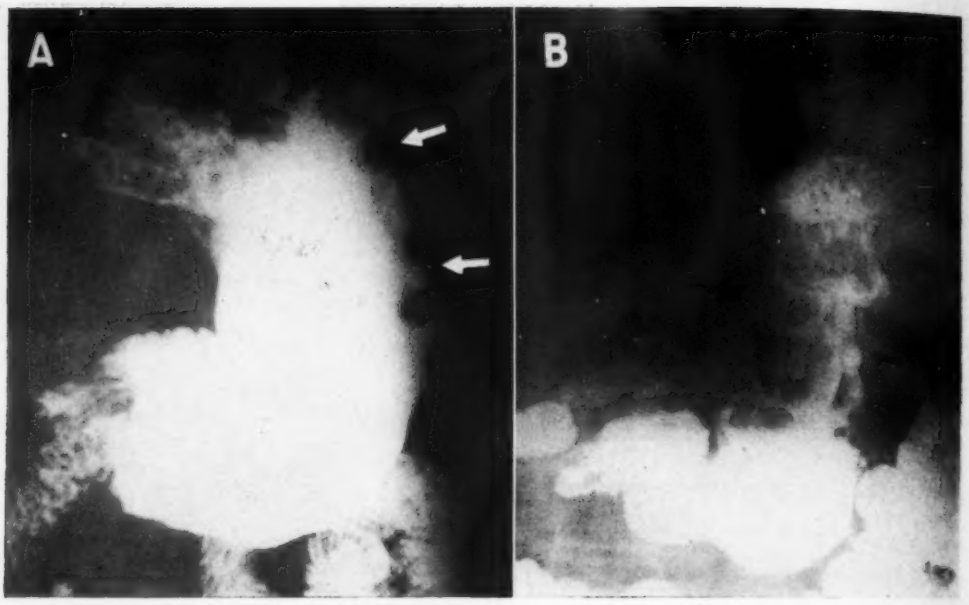


Fig. 1, B–E. Case 1. Later views. Two months after Fig. 1, A, the deformity persisted but there was no progression (B-C). Six months later (D-E) there was marked enlargement of the folds with a pseudo-neoplastic type of filling defect of the greater curvature (arrows).

likewise revealed evidence of markedly enlarged mucosal folds but no ulceration or neoplasm was seen. Two months later another roentgen study of the stomach was made, showing persistence o the unusually marked hypertrophic enlargement of the mucosal folds. There were a pseudo-ulcer filling defect and a large excavated area on the greater curvature of the cardia and fundus. The pylorus was spastic and the duodenal cap presented an irregular filling defect with thickened mucosa. The colon was also spastic. Six months after the original x-ray study, re-examination of the stomach revealed a large neoplastic-like infiltration, invading and reducing the lumen of the stomach.

Comment: In spite of the increasing enlargement of the filling defect and encroachment upon the lumen of the stomach, the patient has progressively gained in weight and strength and has been asymptomatic for over eighteen months. She refused surgical exploration. The x-ray findings were out of all proportion to the clinical manifestations, and a diagnosis of hypertrophic giant mucosal folds was made. Although the diagnosis is still not absolute, the patient's condition in all probability is of a benign nature. Because of the roentgen evidence of extensive



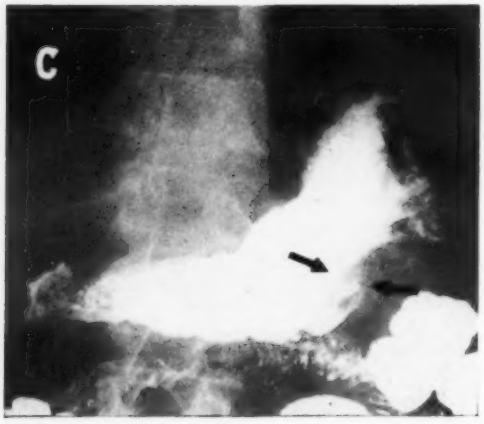


Fig. 2. Case 2. A. Extensive deformity on the posterior wall of the greater curvature. B. Roentgenogram made six months later, in the erect position, showing the extensive filling defect with mucosal changes. C. Partially filled stomach, illustrating the pseudo-ulcer-niche-defect at arrows.

mucosal involvement and hypertrophy, carcinoma was eliminated and the presence of a lymphoblastomatous lesion was strongly considered. Roentgen studies showed a progressive invasive type of filling defect, but no mass could be palpated corresponding to the defect. This finding, too, is consistent with a lymphomatous lesion. Finally, a syphilitic lesion was considered and, although the serologic tests were negative, the behavior of the lesion and the subsequent clinical course suggested this possibility. A diagnosis of giant mucosa was made.

CASE 2 (Fig. 2): A man of 71 complained of abdominal discomfort and indigestion for several months, associated with weakness, anorexia, and loss of weight. For the past five weeks there had been intermittent abdominal cramps and a diarrhea of loose watery stools with mucus but no blood. On physical examination a bilateral inguinal hernia was found. The abdomen and rectum were entirely negative. The red blood cell count was 5,400,000; hemoglobin 92 per cent; white cells 13,000, with a normal differential count; sedimentation rate 18. Stools were negative for blood, and cultures were negative for pathogens. The Wassermann reaction was negative.

A gastro-intestinal roentgen study revealed enlarged mucosal folds with a suggestive ulcerative defect on the greater curvature of the stomach. The duodenal cap appeared regular. A colon enema study revealed no organic lesion. Six months later a check-up examination showed an apparent extensive infiltrative lesion of the fundus and cardia of the stomach with widening of the mucosal folds. One month after this, re-examination by another roentgenologist was also reported as demonstrating enlargement of the gastric mucosal folds. The gastroscopic examination revealed evidence of a gastritis

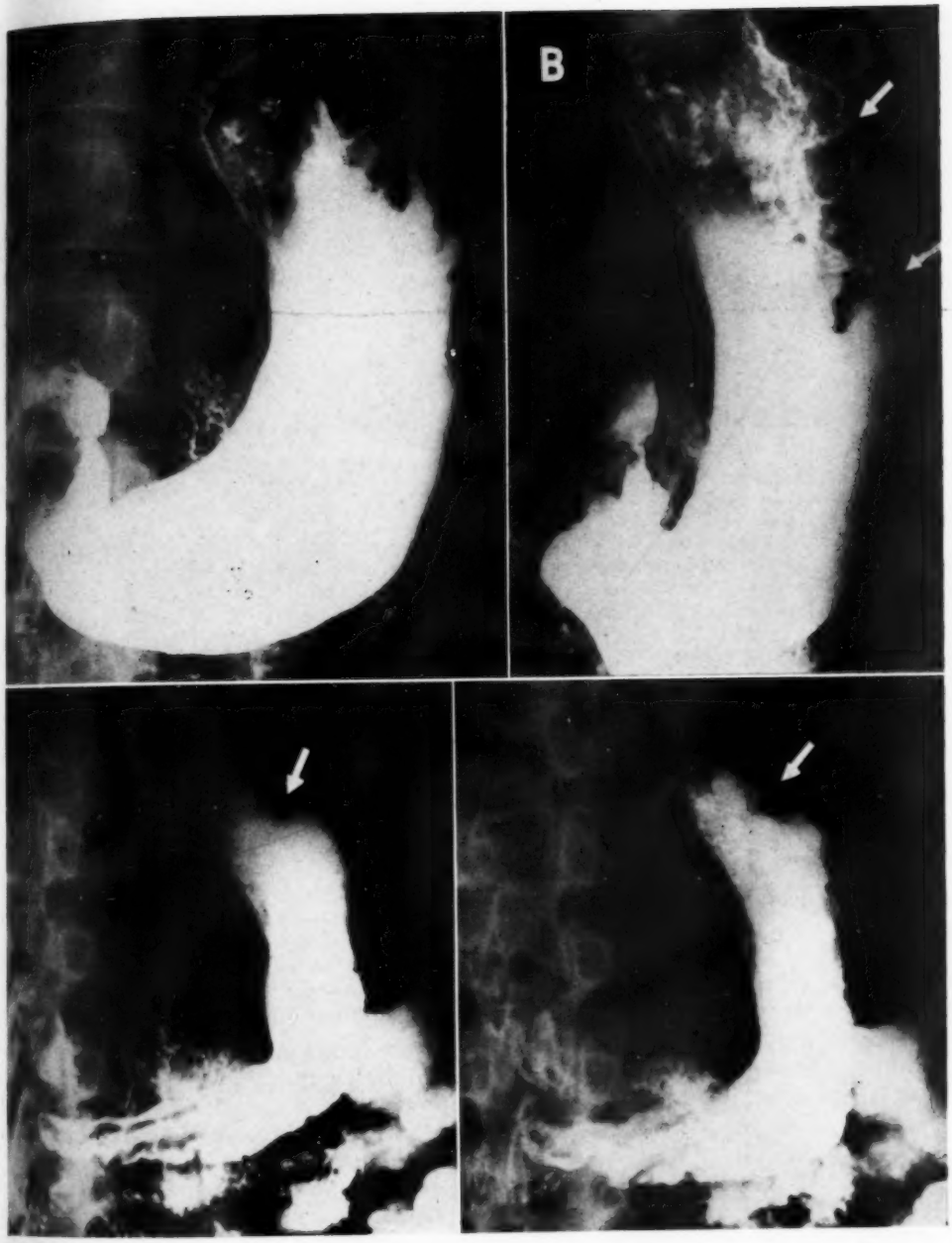


Fig. 3, A-B. Case 3. A. An extensive irregular filling defect is shown on the greater curvature of the cardia and fundus of the stomach. B. Lateral view, presenting greater detail of the mucosal enlargement and deformity (arrows).

C-D. Case 4. Deformity of the greater curvature of the cardia and body of the stomach due to the enlarged mucosal folds.

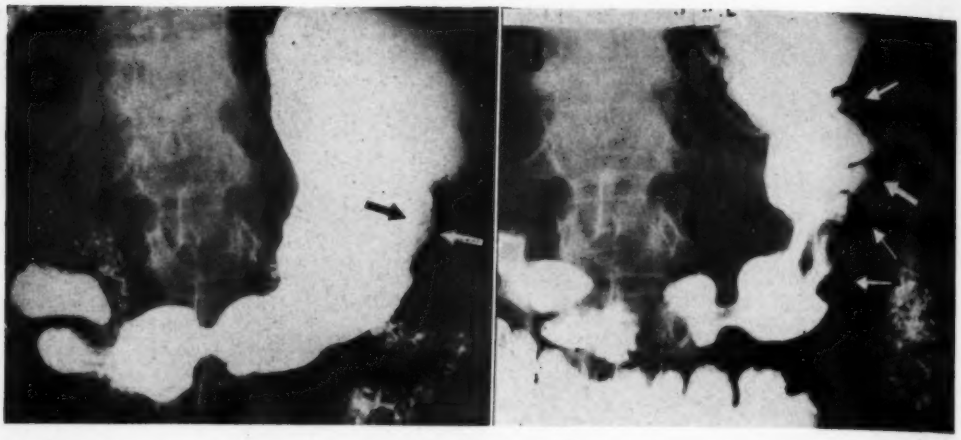


Fig. 4. Case 5. A. Ulcerating type of filling defect on the greater curvature (arrows); also some deformity of the greater curvature of the cardia. B. Same case with small amount of barium, showing a more extensive deformity (arrows).

The patient was placed on medical therapy and has been followed for fifteen months. He has regained his weight, symptoms have disappeared, and there have been no further digestive upsets.

Comment: This case presented a clinical picture of carcinoma, with a short history of digestive disturbance and loss of weight and strength. The x-ray revealed enlarged, widened, and flattened mucosal folds; the greater curvature of the stomach was irregularly deformed and presented a pseudo-ulcer filling defect, which apparently was produced by the enlarged irregular mucosal folds. Cancer was suspected on the basis of the clinical history and roentgen findings but, owing to the presence of enlarged mucosal gastric folds, this diagnosis seemed to be questionable, and further studies were recommended. Since the gastroscopic examination revealed the mucosal changes but no evidence of neoplasm, the roentgen findings were believed to be of a benign character. The subsequent clinical course also suggested the probability of a benign condition.

CASE 3 (Fig. 3, A and B): A man aged 47 complained of pain in the right upper quadrant for ten years. The pain did not radiate and there was no relationship to food. His appetite was good and bowels regular. There was no vomiting. The left kidney had been removed ten years earlier for kidney stones.

A gastro-intestinal roentgen examination showed a deformity on the posterior wall of the greater curvature of the cardia associated with giant mucosal folds. The lesser curvature was regular; the pylorus was spastic; the prepylorus showed a transient narrowing due to spasm. The duodenal cap was normal. A trace of barium was retained in the stomach at the end of five hours. Motility of the intestine was normal; the colon was negative. The extensive filling defect on the greater curvature of the cardia of the stomach was believed to be due to giant mucosal folds.

CASE 4 (Fig. 3, C and D): A man aged 65 complained for many years of digestive disturbances with pain across the abdomen, made worse by eating. There was intermittent diarrhea but no vomiting. The physical examination was negative. A gastro-intestinal roentgen study revealed enlargement of the gastric mucosal folds with a persistent deformity of the greater curvature of the cardia of the stomach which strongly suggested an early neoplastic lesion.

Comment: Cases 3 and 4 presented dissimilar symptoms, but the roentgen findings were characteristic of an intragastric abnormality involving the greater curvature of the cardia and body of the stomach. In each instance the roentgen features simulated a malignant growth. Each presented enlarged mucosal folds. No gastroscopic examination was made. It has been over eighteen months since the roentgen examination, and both patients are asymptomatic.

CASE 5 (Fig. 4): A man aged 60 complained for one year of pain in the epigastrium and back,

intermittent abdominal cramps with gurgling due to excessive gas, vomiting, and loss of weight. There was a marked progressive constipation, relieved by laxatives and enemas. Physical examination showed a palpable mass in the left upper abdomen. Blood examination showed: red cells 4,000,000; hemoglobin 88 per cent; white cells 7,500, differential count normal; sedimentation rate 42. Urine and serologic examinations were negative. Gastric analysis revealed an absence of free hydrochloric acid. Stools showed a trace of blood.

The gastro-intestinal roentgen study demonstrated an extensive deformity of the greater curvature with hypertrophy of the mucosal folds of the cardia and fundus of the stomach. A trace of barium was retained in the stomach at the end of five hours. Twenty-four-hour examination showed a filling defect at the splenic flexure. A barium enema revealed an annular filling defect at the splenic flexure with partial obstruction due to carcinoma. At operation a carcinoma of the colon was resected. The stomach was not opened but was explored and revealed no evidence of gastric disease.

CASE 6 (Fig. 5): A man aged 56 complained of loss of weight and weakness for over one year. During this period a chest film revealed a large mass in the mediastinum and in the right lower lung. There was involvement of the cervical lymph nodes and biopsy revealed metastatic carcinoma. Three weeks prior to a gastro-intestinal roentgen study the patient began to have pain in the abdomen, radiating to the back and associated with severe constipation.

The x-ray revealed an extensive deformity of the greater curvature with unusually broad flattened folds in the fundus of the stomach. The gastric mucosal folds were thinned out and reduced in number. The upper jejunum showed a flattening of the folds, indicating evidence of a nutritional deficiency. A twenty-four-hour examination showed a poorly filled colon. A barium enema revealed an extensive carcinoma of the splenic flexure. At operation the tumor was resected. The stomach was not incised, but exploration revealed no evidence of a gastric lesion.

Comment: Cases 5 and 6 presented roentgen changes in the mucosal folds of the stomach. The folds were widened and hypertrophied. In each, extensive deformity of the greater curvature simulated carcinoma; the colon revealed a carcinoma of the splenic flexure, and the growth was resected. The stomachs were explored but not opened, as nothing was found to warrant incising them. The patient with metastasis to the mediastinum and lung died; the other is living and well ten months after the operation.

Fig. 5. Case 6. An extensive deformity of the greater curvature with marked widening of the mucosal folds.

CASE 7 (Fig. 6, A and B): A woman aged 61 complained for several months of substernal pressure and distress following meals. She felt better when her stomach was empty. There was no vomiting. There were considerable gas and constipation. The physical examination was negative.

A gastro-intestinal roentgen study revealed a small penetrating ulcer defect on the greater curvature. There was an extensive deformity of the greater curvature with marked enlargement of the mucosal folds as a result of a gastritis. The lesser curvature was regular; the pylorus was spastic and the duodenal cap was normal. The colon showed evidence of stasis. A diagnosis of a penetrating ulcer of the greater curvature of the stomach associated with gastritis was made.

Comment: In this case there was an extensive deformity of the greater curvature of the stomach with an ulcer-niche-like filling defect. The picture varied with the state of filling of the stomach. When it was completely filled, there was a concave deformity with an ulcer-niche-like defect projecting out from its center. With partial filling, the entire greater curvature was ragged and irregular. No gastroscopic examination was obtained. The clinical picture was indeterminate,

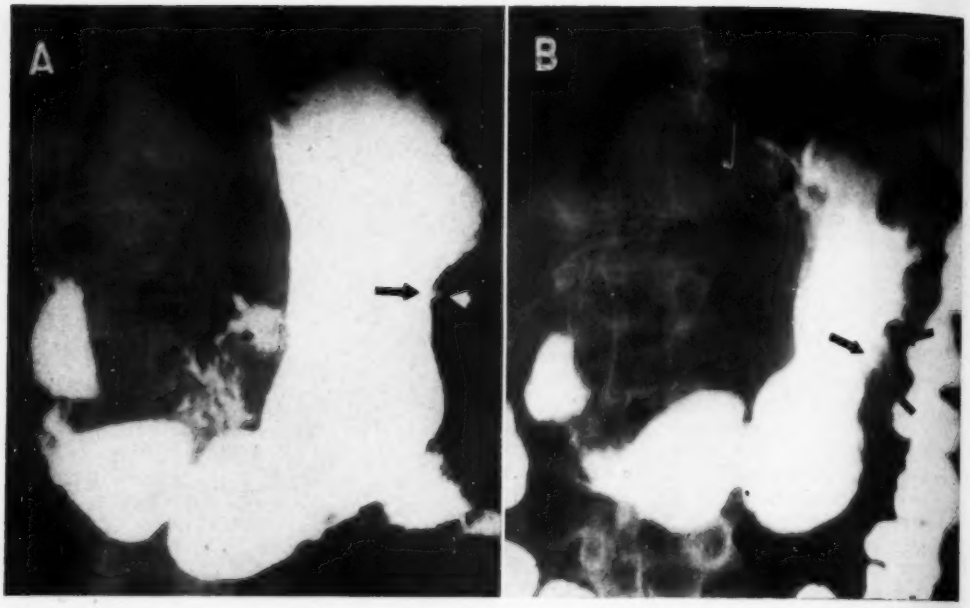


Fig. 6. Case 7. A. An ulcer-like niche defect in an excavated area on the greater curvature (arrows). B. Same case with partial filling of the stomach, showing marked deformity due to enlarged mucosal folds.

and since there was no loss of weight and nothing to indicate a serious gastric disease, the patient was placed under medical therapy and observation. On clinical follow-up examination, eight months later, she was asymptomatic.

CASE 8 (Fig. 7, A and B): A man aged 66 complained of vague stomach disturbances for eleven years, giving a history of periodic episodes of epigastric pain occurring about two hours after meals, nausea, belching, and constipation. His appetite was poor; there was no loss of weight. Two years after the onset of symptoms, x-ray studies revealed a normally functioning gallbladder without stones.

A gastro-intestinal roentgen examination showed marked intestinal stasis but no gastric lesion. The patient's symptoms were relieved and he felt comparatively well until six months later, when digestive disturbances recurred. A gastro-intestinal roentgen examination made at this time revealed an extensive deformity of the greater curvature of the cardia and the fundus of the stomach, with evidence of enlargement of the mucosal folds. A deep penetrating ulcer-niche defect was noted on the lesser curvature of the antrum of the stomach. A diagnosis of a penetrating gastric ulcer associated with gastritis was made.

CASE 9 (Fig. 7, C and D): A man aged 47 gave a history of indigestion for fifteen years, with intermittent pain relieved by food. Physical examination was negative. A gastro-intestinal roentgen study revealed normal emptying of the stomach. The greater curvature was ragged, with deep irregular serrations. A mucosal study showed some hypertrophy of the folds. The lesser curvature was regular. In the erect oblique position a large excavating filling defect with two small niche-like projections was demonstrable. The pylorus was spastic and the duodenal cap markedly deformed due to an ulceration. A diagnosis of duodenal ulceration with associated hypertrophic gastritis was made.

Comment: These two cases, one a gastric ulcer and the other a duodenal ulcer, presented gastric mucosal changes indicating an associated gastritis. Each presented a bizarre appearance of the greater curvature, suggesting an organic gastric disease. Each was due to an associated gastritis. No gastroscopic examination was made. Both patients were asymptomatic one year after the roentgen examination.

SUMMARY

The purpose of this paper is to point out and emphasize the fact that the greatest

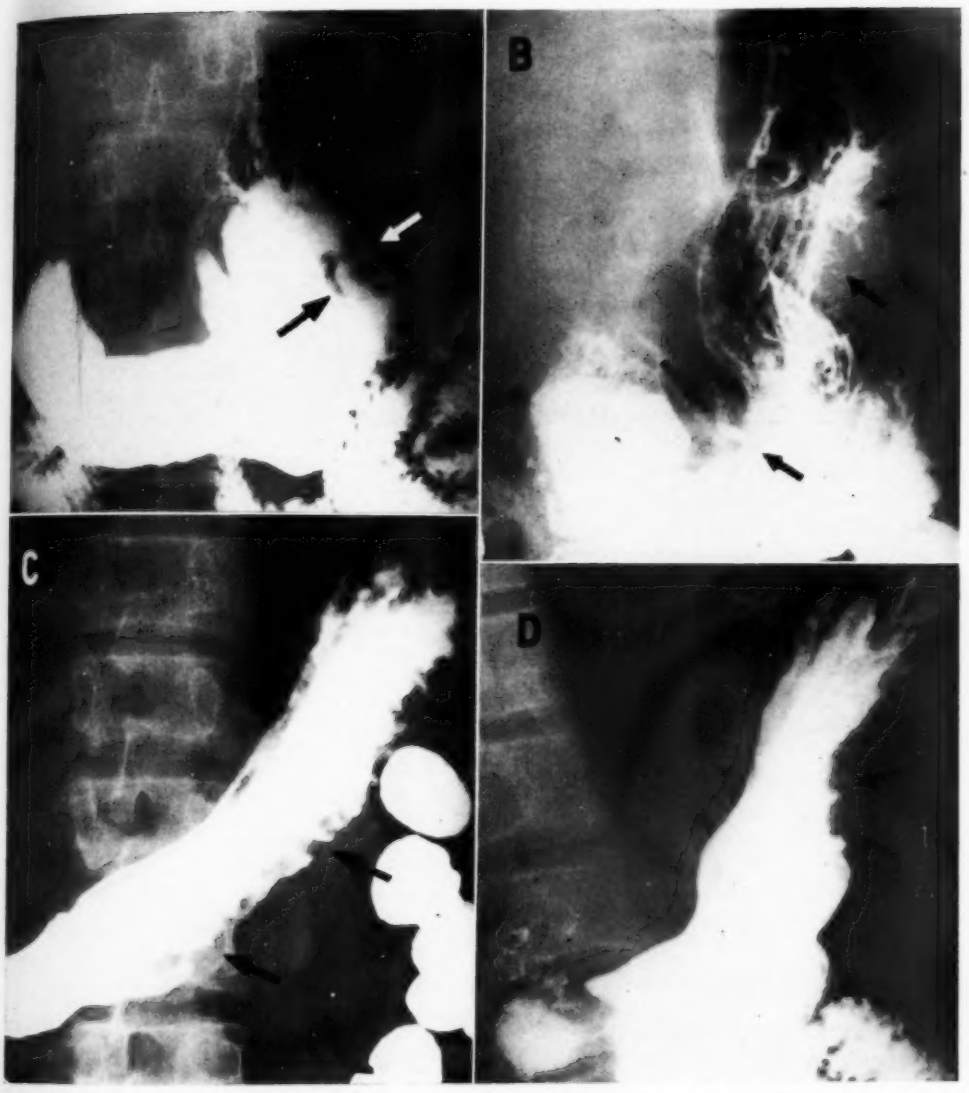


Fig. 7, A-B. Case 8. A. Marked deformity of the greater curvature with a pressure defect due to distention of the splenic colon. B. Roentgenogram made in erect position showing the extent of the deformity on the greater curvature with a deep penetrating ulcer niche on the lesser curvature of the antrum (arrows).
C-D. Case 9. C. Case of duodenal ulceration. Exaggerated serrations or saw-tooth effect of the greater curvature. D. Oblique view showing the deformity of the greater curvature with pseudo-ulcer-niche defects (arrows).

caution must be taken in the interpretation of mucosal abnormalities and filling defects of the greater curvature of the stomach. This is especially important in the cases presenting defects that do not conform to the usual disease pattern. Repeated roentgen studies are essential in all doubtful cases and confirmatory information obtained by thorough clinical investigation and gastroscopic studies is necessary. An unequivocal diagnosis cannot always be made solely on the basis of the gastric roentgen findings. A study of the subsequent clinical developments over a

period of months is essential and often necessary to establish the significance of non-conforming disease patterns presenting deformities of the greater curvature.

A group of unusually interesting cases is presented to illustrate some of the difficulties encountered in the roentgen diagnosis of non-conforming disease patterns of the mucosa of the stomach. The filling defects shown in the roentgenograms were strongly suggestive of a primary gastric lesion. The presence of marked hypertrophy of the gastric mucosal folds is not ordinarily consistent with carcinoma. In carcinoma the folds are usually obliterated. However, these changes could fit into the picture of Hodgkin's or lymphoblastomatous disease and syphilis. Great enlargement of the mucosal folds due to hypertrophy is consistent with benign giant gastric mucosa. Extensive gastric deformity of the greater curvature with unusually marked serrations may be due to a gastritis associated with peptic ulceration.

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DISCUSSION

Kenneth S. Davis, M.D. (Los Angeles, Calif.): Dr. Feldman is to be congratulated for bringing out a problem in differential diagnosis that all of us have encountered. I feel that his paper is timely and thought-provoking. Like Dr. Feldman, we at St. Vincent's Hospital have felt that a gastroscopic study is essential in those cases with borderline and atypical roentgen findings. We also agree with him in insisting on repeat x-ray studies where the roentgen evidence of a lesion is not definite and clearcut.

At times there are lesions of the stomach which cannot be definitely diagnosed even by combined x-ray and gastroscopic studies. We have found that in these cases a peritoneoscopic study, as developed by Dr. Ruddock, is of great help in the differentiation between benign and malignant lesions, as well as in ruling out metastasis.

In this study, which is done on an empty stomach, the patient swallows a duodenal tube with a light bulb at the tip. Peritoneoscopy is then done with the stomach empty. Air is then slowly pumped into the stomach while it is observed under the peritoneoscope. If the lesion in the stomach wall is indurating, this part of the stomach does not expand and the lesion can be localized. When the stomach is partially filled with air, peristalsis can be observed and its presence or absence may be determined in any portion of the organ. When the stomach is well distended with air, the light within the stomach is turned on and the light in the peritoneoscope turned off. This procedure gives a minute and detailed view of the stomach wall. The gastric rugae *when normal* are never visualized, but when hypertrophied they can be plainly seen. The blood vessel markings are closely observed as they are the clue to lesions of the stomach wall. In the presence of an indurating lesion the circulation is definitely interrupted. I believe this procedure is preferable to exploratory surgery as it entails practically no operative mortality.

SUMARIO

Malformaciones de la Mucosa de la Curvatura Mayor del Estómago

Tiene por fin este trabajo señalar y recalcar la suma cautela que hay que mostrar en la interpretación de las anomalías y nichos de la mucosa de la curvatura mayor del estómago, máxime en los casos en que no se conforman al habitual patrón patológico. En todo caso dudoso se imponen repetidos estudios roentgenológicos y se necesitan datos corroboradores aportados por la investigación clínica detenida y los estudios gastroscópicos. No puede formularse siempre un diagnóstico firme a base exclusiva de los hallazgos radiológicos del estómago. A fin de establecer el significado de los patrones patológicos atípicos en las malformaciones de la curvatura mayor el estudio de los fenómenos clínicos subsiguientes durante varios meses resulta indispensable.

Preséntase un grupo de casos por demás interesantes para demostrar algunas de las dificultades con que tropieza el diagnóstico roentgenológico de los cuadros patológicos atípicos de la mucosa gástrica. Los nichos que aparecen en los roentgenogramas son muy indicativos de lesión gástrica primaria. La presencia de hipertrofia pronunciada de los pliegues de la mucosa gástrica no suele ser compatible con carcinoma, pues en éste los pliegues

están casi siempre obliterados. Sin embargo, dichas alteraciones podrían encajar en el cuadro de la enfermedad de Hodgkin (linfoblastomatosis) o de la sífilis. Una gran hiperplasia de los pliegues de la mucosa es compatible con un estado benigno. Una malformación extensa de la curvatura mayor con bordes serrados muy bien definidos puede deberse a gastritis asociada a úlcera péptica.

Carcinoma of the Tonsil

A Review of Treatment and Its Results in a Group of Ninety Cases

JOHN H. WALKER, M.D., and MILFORD D. SCHULZ, M.D.[1]

THE TONSILLAR area is a relatively uncommon site for cancer. Because of this fact, the medical literature contains few reports covering a large number of cases. From the material which has been published (3, 5, 9, 10, 11), it is apparent that the pattern of management of patients with this disease has been fairly uniform for the past fifteen years. Since progress depends on a periodic evaluation of the results of any treatment, it has seemed worth while to review at this time a group of cases with the diagnosis of carcinoma of the tonsil treated with irradiation during the past ten years.

MATERIAL STUDIED

This study is based on all the patients with carcinoma of the tonsil irradiated at the Collis P. Huntington Memorial Hospital from 1936 through 1941 and at the Massachusetts General Hospital from 1936 through 1945. Since the primary site of an extensive tumor in the mesopharynx is often impossible to determine, only those cases in which it was reasonably certain that the lesion was located at the palatine tonsil, the tonsillar fossa, the tonsillar pillars, or in the triangular fold have been considered. Excluding one case in which the tumor later proved to be a Kaposi sarcoma, 90 cases were found and analyzed.

In the series, there were 76 (84 per cent males and 14 (16 per cent) females. The median age was sixty-five, the oldest patient being eighty-seven and the youngest twenty-nine years. These figures correspond with those reported by Schall (9) and Lierle (5), and confirm the common belief that cancer of the tonsil occurs most frequently in males in the seventh decade of life.

Because of the insidious onset of malignant disease, patients almost universally procrastinate in seeking medical advice. The median delay in treatment in this group was three months. The duration of disease (symptomatically) at the time treatment was instituted ranged from one day (?) to over two years. The most frequent presenting complaint was soreness of the throat, which was noted in 54 per cent of the group. Swelling of the neck was the first sign in 46 per cent, difficulty in swallowing in 16 per cent, bleeding in 15 per cent, weight loss in 4 per cent, and hoarseness in 2 per cent. A noteworthy fact is that in only 9 per cent was a growth in the mouth observed.

Lymph-node metastases are often the first indication to the patient that he has the disease. Sixty per cent of the group presented enlarged nodes when they were first seen, and in two-thirds of these the "lump in the neck" was the first subjective sign to be observed. Of those who had no palpable metastases at the time of first examination, 8 per cent later showed cervical lymph node involvement. No attempt has been made to correlate the metastatic spread of the cancer with the grade of malignancy of the lesion, but the evidence suggests that tumors classified as Grade I (Broders) did not metastasize early, although they were locally recalcitrant in responding to irradiation. One patient with transitional-cell carcinoma had generalized metastases when first seen, and in another metastases subsequently developed beyond the cervical nodes. Of the patients with lymphoepithelioma, one had remote disease and three had cervical metastases when first seen.

[1] From the Department of Radiology, Massachusetts General Hospital, Boston, Mass. Accepted for publication in December 1946. Presented at the First Annual Meeting of the Pacific Northwest Radiological Society, May 4, 1947.

HISTOLOGY OF TUMORS
(Table I)

Of the total group, 78 tumors were epidermoid carcinomas of varying grades, 7 were lympho-epitheliomas, 3 transitional-cell carcinomas, 1 a lymphosarcoma, and 1 a reticulum-cell sarcoma. Carcinoma of the tonsil is, as a rule, of a high degree of malignancy, only a small percentage being of the highly differentiated type. In the present series, the 8 per cent of low-grade malignancy corresponds to the incidence reported by Duffy (3) and by Martin and Sugarbaker (6). Taylor and Nathanson (11), on the other hand, reported 17 per cent Grade I lesions.

TABLE I: TUMORS OF THE TONSIL: HISTOLOGIC ANALYSIS

Epidermoid carcinoma	
Grade I	8%
Grade II	28%
Grade III	30%
Grade IV	3%
Unclassified	18%
Lympho-epithelioma	8%
Transitional-cell carcinoma	3%
Sarcoma	2%

TREATMENT

The methods of treatment carried out at the Huntington Memorial Hospital and at the Massachusetts General Hospital have, on the whole, been comparable. Neck dissection was employed in none of the 90 patients in the present series. Already existing metastases, or the fact that the patients were poor surgical risks, precluded attempted cure by dissection.

Adherence to inflexible rules or to definite specifications in radiation therapy is inadvisable. Individual evaluation as to the course and method of irradiation has been the policy in use at both clinics. In general, as much radiation is directed into the tumor as can be safely tolerated by the overlying tissue. In many instances, since palliation only was sought, cancericidal doses were avoided.

During the ten-year period under consideration, both supervoltage and high-voltage therapy were employed. A number of patients received both. Occasional cases in which high-voltage therapy apparently failed were subsequently treated with supervoltage. Especially was this true of patients in whom cervical metastases subsequently developed or cervical metastases already present failed to respond well to the lower voltage. The change to higher voltage was made, for the most part, in an effort to produce as little further damage as possible to previously irradiated skin.

With high-voltage (200 kv.) treatment, the factors used were 50 cm. tube-skin distance, 20 ma., with 0.5 mm. Cu and 1.0 mm. Al filter, half-value layer 0.9 mm. Cu, roentgen output 50 per minute, and portals adequate to cover the disease, sparing as much normal tissue as possible. Ordinarily two opposing portals were employed, supplemented in some cases by an intra-oral cone at 30 cm. distance.[2] The optimum dose appeared to be 3,000 to 4,000 r, measured in air, through each side, at the rate of 300 r per day. When an intra-oral cone was used, an additional 2,500 to 3,000 r were delivered at 300 r per day

With supervoltage (1,000 kv. at Huntington Hospital; 1,200 kv. at Massachusetts General Hospital), the tube-skin distance was 70 cm. and the half-value layer was 9.0 mm. Cu. Treatments were given daily at the rate of 300 to 400 r per treatment through a single lateral portal. A total dose varied from 2,400 to 6,600 r, the optimum dose being considered to be 6,000 r, measured in air, at the skin level.

Twelve patients received interstitial radiation in conjunction with roentgen therapy. In some cases, this additional treatment was administered to the primary lesion, in others to lymph nodes involved by metastases.

A routine procedure followed in this clinic is the extraction of remaining teeth, prior to irradiation, in patients with poor oral hygiene, or even when the remaining

[2] Treatment with the intra-oral cone was employed in those cases in which it was mechanically possible to introduce it, and in which the primary disease could be covered with the cone.

TABLE II: TUMORS OF THE TONSIL: OVERALL SURVIVAL

Years Survival	No. Patients with Opportunity to Survive	No. Patients Who Survived
1	79*	42 (53%)
2	66	26 (39%)
3	56	14 (25%)
4	49	9 (18%)
5	39	6 (15%)
6	25	3 (12%)
7	21	3 (14%)
8	15	2 (13%)

* Eleven patients did not have opportunity to survive 1 year and are not included in this analysis.

teeth are healthy. This is based on the well accepted fact that teeth undergo definite changes when exposed to x-rays or to gamma radiation (2, 8). The patients, as a rule, are co-operative when adequate explanation is offered them.

RESULTS OF TREATMENT

At the end of the year 1945, of the 90 patients included in the study, 48 were known to be dead, 11 were untraced, and 31 were known to be alive. In the analysis of results of treatment, the 11 untraced patients are counted as having died of cancer as of the date of the last observation; 8 had evident disease at that time. Of the 48 known dead, 37 died of cancer, 6 died of intercurrent disease (5 of these, however, had recognized residual cancer), and in 5 the cause and date of death could not be determined. Ten patients are alive with evident disease, and 21 are alive without apparent disease.

Of the patients who have had a chance to survive five years or more (*i.e.*, were treated five or more years ago), 6 or 15 per cent have done so (Table II). One of these has since died of pulmonary metastases. Of 21 patients who had an opportunity to live seven years or more, only 3 have survived that length of time. At the end of the first year after treatment, 47 per cent had succumbed to their disease.

Of the 21 patients alive and free of disease at the close of 1945, in 3 the period since treatment is less than one year; in 5, it is one to two years; in 3, two to three years; in 4, three to four years; in 2, four to five years; and in 4 over five years have elapsed since treatment. The longest survival, with freedom from disease, is eight years. The longest survival among the 10 patients living with disease is five years.[3]

ANALYSIS OF RESULTS OF TREATMENT

Histology of Tumors: Analysis of the results of treatment on the basis of the histology and grade of the lesion indicates that prognosis cannot be made on the grade of the tumor alone. The tumors histopathologically classified as lympho-epithelioma, as a whole, responded more favorably to treatment than did the epidermoid carcinomas, the transitional-cell carcinomas, or the lymphosarcomas. Of 7 patients with epidermoid carcinoma Grade I, none has lived longer than eighteen months, and control of the local disease has been poor. All of the patients with epidermoid carcinoma who survived two years or more had Grade II and Grade III lesions. In some cases with fairly small primary lesions the local disease failed to be controlled, while in others with larger tumors of the same histologic grade the primary lesion was controlled without difficulty. Sixteen patients who had epidermoid carcinoma are living without disease with an average survival of thirty-nine months; 8, alive but with clinical evidence of disease, have an average survival of nineteen months.

In 6 of the 31 living patients, the tumor was lympho-epithelioma. This type of tumor has shown a most gratifying response to treatment. In contrast to the observations of Martin and Sugarbaker (6) that for a patient with lympho-epithelioma the duration of life from the onset of symptoms was only twelve months, in this series it was found to be over thirty months. This was true in those surviving with disease as well as those who have remained free of disease.

Of 3 patients with transitional-cell car-

[3] This patient has since died, sixty-three months after treatment.

TABLE III: TUMORS OF THE TONSIL: ANALYSIS WITH RESPECT TO METASTASES

Years Survived	With Metastases (At Time of Treatment)			Without Metastases		
	No. with Opportunity to Survive	Survived No.	Survived Per Cent	No. with Opportunity to Survive	Survived No.	Survived Per Cent
1	46	20	43	33	22	66
2	41	13	32	25	13	52
3	34	7	21	22	7	32
4	29	4	14	20	5	25
5	23	2	9	16	4	25

cinoma, one is alive twenty-six months after treatment but with questionable disease in the neck; two are dead of generalized metastases twenty-one and twenty-six months, respectively, after the initial therapy. Both patients with sarcomatous lesions are dead: the one with lymphosarcoma survived twelve months; the other, with reticulum-cell sarcoma, died fourteen months after institution of treatment.

Metastases: The presence or absence of metastases, as might be suspected, played an important role in the control of the tumor. Table III shows the comparative survival rates for patients with and without metastases at the beginning of treatment. Of those free of metastases when first seen, 66 per cent survived the first year after treatment, whereas only 43 per cent of those with metastases lived this length of time. Twenty-five per cent of those without metastases, who had an opportunity to do so, survived five years as compared with but 9 per cent of the metastatic group. The primary lesion, as a rule, responded to treatment more readily than the metastatic lymph nodes, with the exception of regional cervical metastases from lympho-epithelioma.

Combined Radium and Roentgen Therapy: In the group studied, no striking advantage was evident from the use of radium as an adjunct to roentgen therapy. In one of the 12 cases so treated, interstitial radiation and x-rays were employed to control recurrence three years after surgical removal. This patient has survived more than five years without clinical evidence of disease. The average survival of the other 11 patients in the group is 14.5 months as compared with an average survival of 21.5 months for the entire series, and 12.5 months for those known to be dead. In other words, the results in patients treated in this clinic by interstitial and external irradiation are no better than those in patients treated by external irradiation alone.

Supplementary External Irradiation: The question as to the value of supplementary external irradiation in those patients in whom the primary disease was not controlled by the initial course of treatment, or in those who subsequently had a recurrence, is a difficult one to answer. The small number of cases makes consideration of individual results almost a necessity.

Of 12 patients who lived four years or more, 3 required further treatment two to three years after the initial course. One of the 3 survived an additional three years, at the end of which time he died of remote metastases; 2 are still alive and free of disease five years after the second course of treatment. One of the latter two had an uvulectomy and interstitial irradiation at the site of recurrence followed by external irradiation. In the second patient, the recurrence was controlled solely by intensive intra-oral high-voltage therapy.

Three of the 26 patients who survived two years received secondary courses of external irradiation six, eleven, and twenty-four months after their initial treatment. One has since died of his disease; one is free of disease; and one shows questionable disease in a cervical node.

As a whole, patients with recurrence within the first six to twelve months after irradiation were not benefited by further treatment. When, however, recurrence did not appear until more than one year

TABLE IV: TUMORS OF THE TONSIL: COMPARISON OF RESULTS OF SUPERVOLTAGE AND HIGH-VOLTAGE TREATMENT

Years Survived	Supervoltage Radiation			High-Voltage Radiation		
	No. with Opportunity to Survive	Survived No.	Survived Per Cent	No. with Opportunity to Survive	Survived No.	Survived Per Cent
1*	36	21	58	43	21	49
2	30	13	43	36	13	36
3	28	9	32	28	5	18
4	26	6	23	23	3	13
5	21	5	24	18	1	6

* Eleven patients treated during 1945 are excluded from this analysis.

after the initial treatment, supplemental treatment appeared to be of definite value.

Comparison of Supervoltage and High Voltage Treatment: Because of reports from other clinics of the great advantage offered by supervoltage as compared to lower-voltage treatment, especial interest was taken in comparing the results of these two methods of irradiation. Of the entire group, 50 patients were treated with high-voltage and 40 with supervoltage radiation. Table IV shows the survival rates in the two groups. Over the ten-year period, for patients having the opportunity to live five years, the percentage of survival was 24 in the group treated with supervoltage and 6 in those receiving high-voltage therapy. The difference between these figures is significant but, in evaluating them, other factors should be borne in mind. First, the number of cases in each group is not large. Second, a division of the ten-year period into two five-year periods showed that, while in the first five years, the survival rate with supervoltage was more favorable than that with high voltage, in the second period the results were roughly comparable. This shift in values is due primarily to a gradual improvement in the method of treatment with high-voltage radiation. Holmes and Schulz (4) report a five-year survival rate with supervoltage therapy of 21 per cent and conclude that this form of irradiation warrants further trial in carcinoma of the tonsil.

DISCUSSION

In the relatively few large series of carcinoma of the tonsil published in recent years (1, 3, 5, 6, 7, 9, 10), the five-year survival rates, ranging from 10 to 17 per cent, are comparable with the 15 per cent rate in the present group. It is significant, however, that in this series almost equally satisfactory results have been obtained without supplementary surgical procedures, and that in comparable cases no appreciable advantage has been observed with the use of interstitial radium.

The use of telecurietherapy, interstitial irradiation, and x-ray irradiation, separately or in combination, is advocated by various observers. Some also support neck dissection in selected cases. Taylor and Nathanson (11) postulate that neck dissection is indicated when lymph node metastasis follows an apparent complete regression of a primary tumor which had previously displayed no evidence of such metastatic involvement. The question therefore arises as to whether any single procedure, or even several procedures, can offer increased life expectancy to the patient with a malignant tonsillar tumor beyond that afforded by x-ray alone. Since each case must be considered individually, no comprehensive statement would be valid. In isolated instances, in which a cervical node has appeared following adequate control of the primary lesion that had not previously metastasized, subsequent surgical or interstitial treatment may be required. In general, however, the results of x-ray treatment alone have been as satisfactory as those from any other single procedure or from a combination of several.

Unfortunately, in many cases the disease is so advanced that only palliative treat-

ment is feasible. The age of the patient (34 per cent of the present group were over seventy years old) frequently prevents the employment of as intensive doses of radiation as might otherwise be indicated. Palliative therapy occasionally adds several comfortable months of life and consequently is to be encouraged even though the prognosis is apparently hopeless. Carcinoma in an advanced stage may in rare instances respond in an unexpectedly favorable manner, both the primary tumor and the metastatic nodes grossly disappearing.

Because certain tumors prove to be unusually radiosensitive, it does not follow that they should receive less than the maximum tolerated dose of radiation. On the other hand, over-irradiation must be guarded against. In attempting to control extensively infiltrating cancer (often complicated by infection), necrosis, slough, and fistula formation may occur after even minor doses of radiation.

SUMMARY AND CONCLUSIONS

1. Ninety unselected cases of cancer of the tonsil treated by irradiation have been presented. The five-year survival rate of 15 per cent is comparable to, but has not surpassed, results generally reported. The results of palliative therapy have been very satisfactory.

2. From the evidence presented, the grade of the lesion has not proved to be of great prognostic significance, except that tumors of low grade were controlled with difficulty. Lympho-epitheliomas appeared to respond well and have warranted in this small group a less guarded prognosis than other types of tonsillar cancer. This may be due to the fact that their rapid growth leads the patients to seek treatment before remote metastases have developed.

3. The presence of metastases necessitates a guarded prognosis in respect to five-year survival, but it should not discourage the use of intensive irradiation, since a certain number of patients respond well to treatment.

4. As compared with treatment without radium, interstitial radium insertion has produced no noticeable improvement in results. External irradiation, adequately given, seems to be the treatment of choice in most cases of carcinoma of the tonsil.

5. In the group studied, supervoltage irradiation has produced a significant increase in the percentage of five-year survivals as compared with high-voltage therapy.

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SUMARIO

Tratamiento del Cáncer de las Amígdalas

Preséntanse 90 casos, sin seleccionar, de cáncer amigdalino tratados con la irradiación (roentgenoterapia de supervoltaje o alto voltaje, con radio por vía intersticial

en algunos casos). El coeficiente de 15 por ciento de sobrevivencias de cinco años es comparable con los resultados comunicados generalmente, pero no los supera. El resultado de la terapéutica paliativa ha sido muy satisfactorio.

A juzgar por los datos presentados, el grado de la lesión no tuvo mayor importancia en el pronóstico, salvo en que los tumores de grado bajo fueron cohibidos con dificultad. Los linfoepiteliomas aparentemente respondieron bien y justifican, en lo relativo a este pequeño grupo, un pronóstico menos reservado que en otras formas de cáncer de las amígdalas, quizás debido a que su rápido desarrollo hace que los enfermos busquen tratamiento antes de presentarse metástasis remotas.

La presencia de metástasis impone un pronóstico reservado con respecto a sobrevivencias de cinco años, pero no debe desalentar el empleo de la irradiación intensa, dado que cierto número de enfermos responden bien al tratamiento.

Comparado con el tratamiento sin radio, la introducción intersticial de radio no mejoró mayor cosa el resultado. La irradiación externa, adecuadamente administrada, parece ser el tratamiento de elección en la mayor parte de los casos de carcinoma amigdalino.

En el grupo estudiado, la irradiación de supervoltaje, comparada con la de alto voltaje, logró un aumento significativo en el porcentaje de sobrevivencias de cinco años.

Gout: Clinical, Pathologic and Roentgenographic Observations

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WHILE IT IS true that gout often goes undiagnosed and much needs to be done toward educating American physicians to recognize this disease, nevertheless progress has been made. This progress has had a distinct bearing on roentgenology, for important developments in the clinical and pathological fields have greatly improved our ability to interpret roentgenographic findings in patients with this disease. In this paper, we shall outline briefly some historical features regarding roentgenography in gout. We shall also describe some significant developments concerning clinical and pathologic aspects of gout and relate these to the principles of roentgenology which are pertinent to the diagnosis of this condition.

HISTORICAL

The use of the roentgen rays as an aid in the diagnosis of gout was first reported by Huber (1). That writer, in 1896, published a reproduction of a roentgenogram which illustrated the lesions produced by gout in one case. Circular zones of translucency in the subchondral bone were demonstrated and their probable relationship to the deposition of urates in the affected tissues was discussed. Hypertrophic spurs, partial or complete destruction of some joints, and subluxations were described

A very large number of publications have, since that time, referred to the roentgenographic phenomena associated with gout. This literature is not reviewed here in detail. It seems appropriate, however, to mention the contributions of a few outstanding writers.

Points of distinction between the roentgen changes which are to be seen in gout and those encountered in patients with rheumatoid arthritis were described in 1905 by Strangeways and Burt (2). Their observations were based upon a comparison of roentgenograms from a hundred gouty and a hundred rheumatoid patients. Findings which were described as characteristic of gout included increased density of bone, bony additions about joints, nodes on the shafts of phalanges, spurs about the heads of the long bones, loss of cartilage, erosion of bone, transparent areas, and dislocations. There were some instances of complete disorganization of bones and even of bony ankylosis.

Strangeways and Burt conducted this study with great thoroughness but unfortunately omitted a correlation of roentgenographic findings with the clinical aspects of the cases. As a result, roentgenographic changes which they encountered in advanced stages of gout were subsequently considered characteristic of all gouty joints.

It remained for Jacobsohn (3) to point out, in 1913, that roentgenograms should not be relied upon to distinguish gout from other forms of arthritis in every instance. In some cases of gout he found changes which closely resembled those encountered in other diseases of joints, but in certain instances lesions which are not to be seen in any other form of joint disease, notably semicircular or oval zones of destruction irregularly disposed about affected joints, were present. Jacobsohn also described cases in which the lesions produced by gout resembled enchondromas and noted the shadows which are cast by subcutaneous tophaceous deposits.

Interesting American studies of the

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roentgenographic phenomena associated with gout were reported in 1919 by McClure (4) and in 1920 by McCarty (5). The presence of focal areas of decreased density was the only change present in some cases. Variable degrees of osteoporosis, narrowing of joint spaces, and bony proliferations were noted. No definite relationship between the duration of the symptoms and the character of the roentgenographic changes was observed.

Upon these foundations, and upon the observations which have been reported in many additional worth-while papers, a more complete and more useful concept of the place of roentgenograms in the diagnosis of gout may now be constructed.

THE LIFE HISTORY OF GOUT

Knowledge relative to the clinical course of gout has been greatly advanced in recent years. Many of the vague, outmoded notions which were handed down to us from previous centuries have been discarded as the life history of this disease has been more clearly outlined.

It is now evident that the symptoms of gout generally progress in an orderly and developing pattern, which may be considered as including (*a*) a larval period, (*b*) a period of acute articular attacks, and (*c*) a period of chronic articular gout, occurring in that order.

The larval period, which is of varying duration, precedes the clinical evidence of articular involvement. Since the specific pattern of disordered chemistry which constitutes the basic anomaly of gout is either inherited or develops very early in life, the larval period may date from birth. During this period gout is usually asymptomatic, although there may be attacks of renal colic as a result of the passage of calculi. The level of blood uric acid may be elevated, and rarely one may find subcutaneous tophi.

The advent of articular attacks should be considered as marking the opening of the second period of gout. These attacks, which characteristically have their onset in the third to the sixth decade, are acute, self-limited, and of varying intensity. They tend to appear without premonition and often affect a bunion joint primarily. Involvement of the bunion joint is not by any means a regular feature of the early attacks, however, as almost any of the joints of the extremities save shoulders and hips may be the initial site.

The onset is occasionally nocturnal but may occur during the day. Early attacks generally remain monarticular, but a series of two or more joints may be affected. Pain is variable, being moderate in some and violent in other instances. Early attacks usually subside within a few days, or at most within a few weeks, although there is a tendency for the attacks to be more prolonged as their number increases.

If the patient is not treated effectively, attacks may recur at intervals of months or years during the second period, tending to involve additional joints.

Hyperuricemia is more frequently encountered during the second period than during the larval period but is not constant during this or during any of the periods of gout. Tophi are encountered with increasing frequency after the onset of the articular attacks. Renal colics may occur in the second period and there is also a notable tendency to episodes of olecranon bursitis.

In persons who have had numerous and prolonged articular attacks, non-remitting joint deformities may appear, marking the advent of the third and final period of gout. Once developed, these deformities persist until death unless corrected surgically. In some cases, serious crippling may result, and further acute inflammatory episodes may also be observed in the chronically deformed joints.

Chronic deformities of the third period of gout are often typical in appearance, being markedly asymmetric. In some instances, however, these are symmetric and may resemble somewhat the deformities produced by chronic rheumatoid arthritis.

Chronic nephritis, recurring renal colics, and extensive deposits of tophaceous material may be encountered during the third

period. Subcutaneous tophi may assume huge proportions and by centrifugal growth may destroy the overlying integument, producing sinuses which discharge crystalline urates and also necrotic matter. The sinuses may become infected, after which repeated healing and opening may be observed. Even at this late stage, hyperuricemia is not a constant feature of the disease.

THE PATHOLOGIC PHYSIOLOGY OF GOUT

Gout appears most likely to be the result of a disturbance in the chemical mechanisms by which the body handles and disposes of uric acid. This has been evident for nearly a century and a half, since Wollaston demonstrated urates in tophaceous material in 1779. The exact nature of the anomalous uric acid metabolism is, however, not yet clearly understood. Proof is lacking that the gouty patient is deficient in ability to excrete or to destroy urates. No decisive evidence has been found to indicate that these persons produce more uric acid than is produced by normal individuals.

As no more promising direction has been suggested for such studies, researches regarding the metabolic defect will necessarily continue to explore the field of urate metabolism in a search for a solution to this mysterious feature of gout.

PATHOLOGY OF GOUT

A unique and specific lesion, the gouty granuloma, is characteristically present in tissues affected by gout. The histologic features of the lesion are fundamentally similar in such different sites as the cartilages of the ear, the olecranon bursae, the kidney parenchyma, and various parts of affected joints. Similar lesions have occasionally been observed in the tongue, the myocardium, and even in the valves of the heart. This pathognomonic lesion is readily discernible in properly prepared histologic specimens.

The gouty granuloma consists of three regions: (*a*) a central zone, in which are deposited crystalline urates, cholesterol, and debris of necrotic tissue; (*b*) surrounding this central zone of caseation and crystals, an inflammatory region of varying cellularity; (*c*) beyond this, a stroma or supporting tissue of varying fibrous density (Fig. 1).

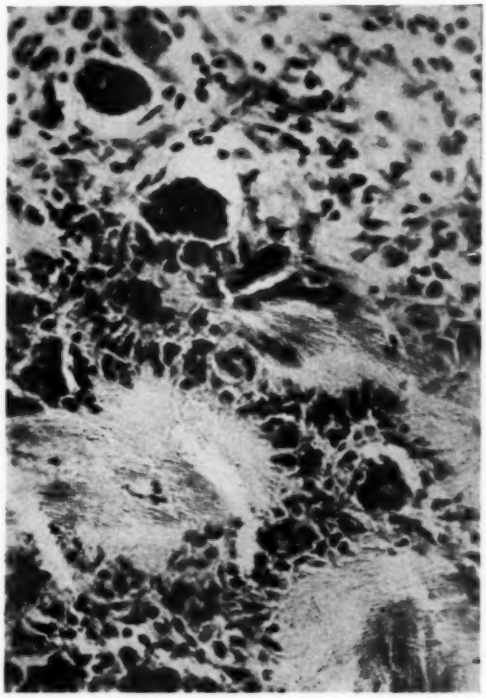

Fig. 1. Gouty granuloma, showing necrotic central zones, surrounded by inflammatory cellular layer. A number of giant "urophages" are present. ×145.

The inflammatory cellular layer adjoining the central zone resembles the cellular layer which may be seen about the necrotic centers of true tubercles, consisting of reticulo-endothelial cells, lymphocytes, and plasma cells. The cellular content of these lesions differs from that of tubercles, however, by the presence of giant reticulo-endothelial cells, some of which incorporate huge numbers of nuclei in a single protoplasmic agglomeration. Some of these cells ingest bundles of urate crystals or incorporate them in the cytoplasm. Because of this phenomenon, these giant cells have been called "urophages."

The histogenesis of the gouty tubercle is

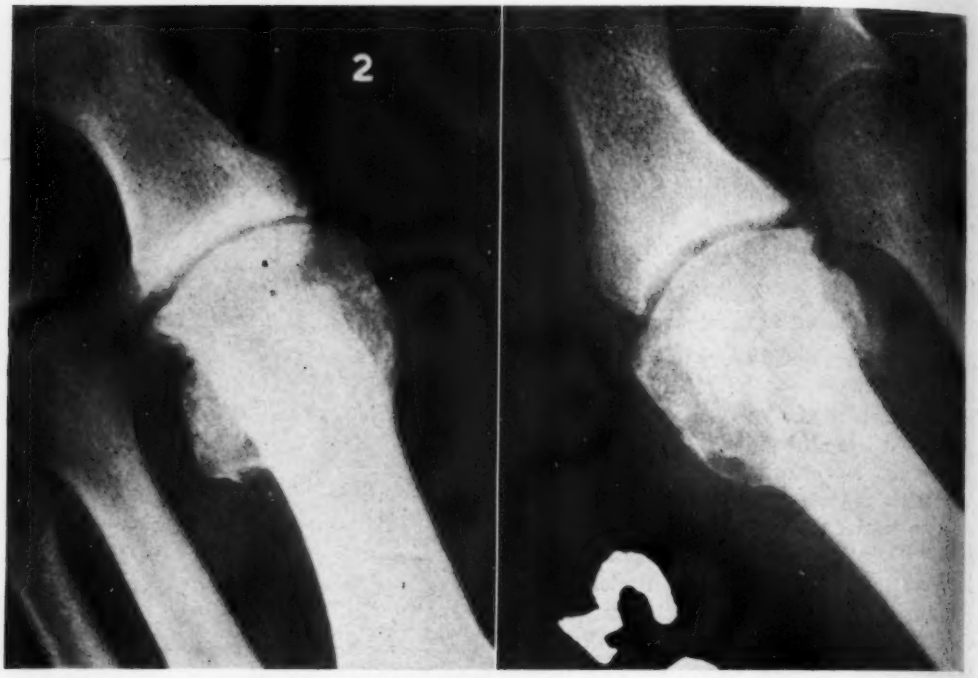

Fig. 2. A zone of osteoporosis on the medial aspect of the base of the first metatarsal bone and first phalanx is the earliest roentgen evidence of gout.
Fig. 3. A cystic lesion in the head of the metatarsal bone.

apparently as follows. The crystals are deposited first. Evidently, these are quite toxic and cause the death of adjoining cells. Degeneration and necrosis then ensue to produce the central caseous-crystalline zone. The presence of this necrotic material brings forth a foreign-body reaction in the surrounding tissues, thus producing the cellular layer. An attempt occurs to wall off this zone of inflammation by means of fibrous tissue, and the resulting fibrosis constitutes the third or supporting layer.

The synovial membrane reacts to the presence of gouty tubercles by thickening and pannus formation. In location and general form, this pannus does not differ from that to be observed in rheumatoid and tuberculous arthritis, but gouty pannus is distinctively encrusted with urates. It may cover the entire cartilaginous surface of a joint and give to the interior an appearance of having been smeared with coarse white paint.

Gouty tubercles form also in the osseous tissues at the ends of bones. These may expand by centrifugal growth, join with the tophi of the synovial membrane, and bring about a more or less complete destruction of the joint.

Similar lesions form in the capsules of joints. Here the tubercles cause a thickening and loss of pliability. This capsular thickening is to some extent responsible for the deformity and loss of mobility which one encounters in chronic gouty arthritis. When gouty tubercles form in kidneys, the resulting foreign-body reaction destroys the normal architectural arrangement of the kidney and brings about the diseased state which may be designated gouty nephritis. In bursae, thickening and fibrosis are produced.

ROENTGENOGRAPHIC OBSERVATIONS

The roentgenographic findings in a patient with gout are dependent upon the

Fig. 4. Narrowing of the joint space is present at the interphalangeal joint of the right great toe. This joint also shows marginal hypertrophy and semicircular and circular translucencies. Destructive lesions are more advanced in the interphalangeal joints of the first toes than in the metatarsophalangeal joints.

state of advancement of the pathologic changes which have been described above. Although pathologic changes do not always exactly parallel the clinical stage of the disease, gross parallelism is usually evident.

In every series one must expect to find a considerable number in whom roentgenograms of joints previously affected by gouty attacks are negative. Such negative roentgenograms will be found in cases in which the pathologic lesions are slight, usually in persons who have had few attacks.

The speed of progression of the pathologic lesions is widely variable in different individuals, and a corresponding wide variability is encountered in the roentgenographic observations in different cases. Some persons in the second period have recurrences of acute articular attacks only at long intervals, of years or decades. In these cases, pathologic developments are long delayed, and roentgenographic changes are slow to appear. In other instances the disease runs a more virulent or malignant course. Such patients suffer from a large number of attacks within a few years, have rapidly developing pathologic lesions, and enter the third period, with its articular destruction and larger subcutaneous and articular deposits of urates, relatively early.

The earliest roentgen evidence of changes resulting from gout is not to be expected until fairly late in the second period and should be looked for in the bunion joint. The first notable change is the appearance of a zone of osteoporosis on the medial aspect of the base of the first metatarsal bone and first phalanx (Fig. 2).

As the gouty process becomes more extensive, this zone of osteoporosis becomes

Fig. 5. Extensive destruction of the metatarsophalangeal joint. The numerous areas of cystic caries produce a honeycomb effect.

frankly cystic. At the sites of such lesions, the bony structure is completely obliterated and roentgenograms consequently show a "punched out" appearance (Fig. 3).

The next stage of gouty destruction results in narrowing of the joint spaces as a result of erosion and obliteration of cartilages by the gouty pannus. Because this process is uneven, surfaces of joints sometimes become markedly irregular. Continued use of such joints produces traumatic effects, as a result of which marginal hypertrophic changes appear (Fig. 4).

An even more destructive effect may be seen where tophaceous deposits in the ends of bones expand greatly. These lesions may cause widespread obliteration of the epiphyses and joints (Fig. 5). Entire joints may disappear at such sites leaving bony stumps projecting into a formless tophaceous mass (Fig. 6). In some advanced instances, one sees the results of combined processes, including erosions, marginal proliferations, and fractures of remaining shreds of bone structure.

An occasional result of large uratic deposits in epiphyseal regions is expansion of the cortex of bones (Fig. 7). This may produce an appearance in the roentgenograms resembling somewhat the picture seen when certain tumors of bone produce expansile effects; *e.g.*, giant-cell tumors or osteogenic sarcomas.

Fig. 6. The entire joint between the first and second phalanges of the fifth finger has disappeared, leaving the bony stumps projecting into the tophaceous mass.

Negative roentgenograms of joints do not necessarily exclude the presence of gouty lesions. If pannus formation predominates and if this process is not accompanied by invasion of the epiphyseal bone by gouty lesions, fairly extensive pathologic lesions may be present in joints which cast no abnormal shadows.

In a joint which has been the site of an acute attack of gouty arthritis, osteoporosis may appear very rapidly. This is especially apt to be observed when, as a result

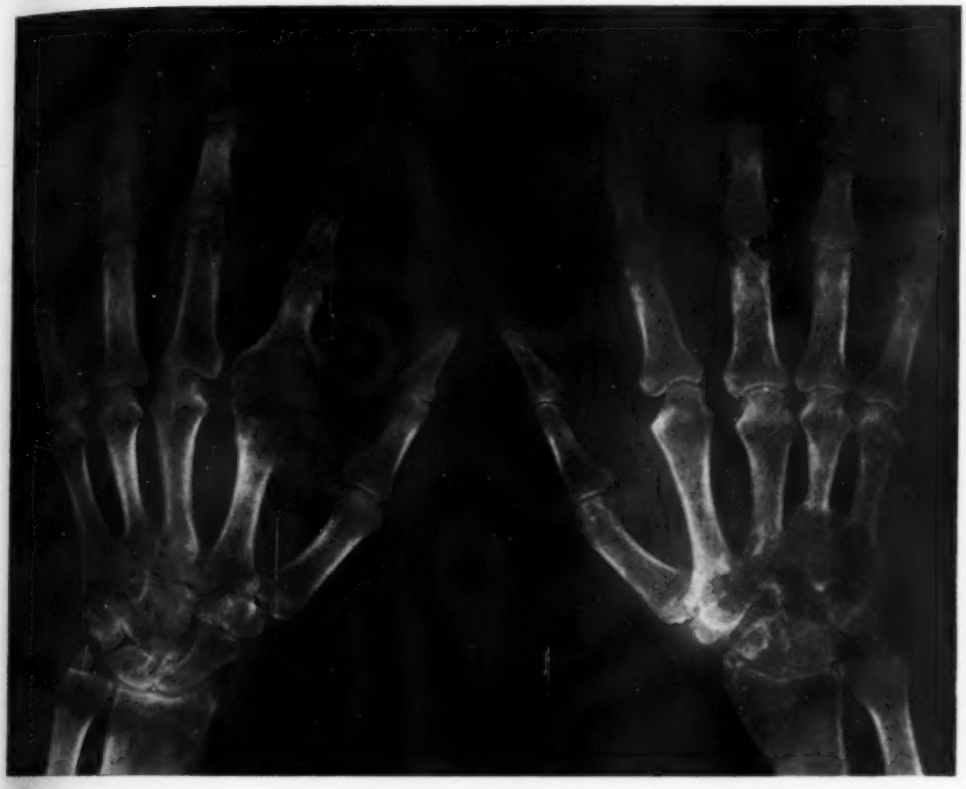

Fig. 7. Expansion of the cortex of bones produced by tophaceous deposits. These lesions may resemble the expansile lesions observed in certain tumors of bone.

of misdiagnosis, patients are kept immobile in bed for exceptionally long periods. The effects of the acute localized inflammation and disuse may then bring about widespread atrophy. There may be no other evidence of gouty destruction, so that atrophy of bone may be the only visible roentgenographic abnormality.

When the roentgenologist encounters patients with joint disease associated with amputation of some portion of an extremity, the diagnosis of gout should be recalled. Amputations are occasionally required in this disease because of the presence of stubborn draining sinuses or seriously crippling deformities which interfere with the proper use of an extremity.

Tophi have been referred to as "chalk stones" because of the white, chalky appearance of their contents. This material does not contain notable quantities of calcium, and tophi are consequently not particularly radiopaque. In consequence of this, larger tophaceous masses cast only evenly dense roentgenographic shadows, the opacity of which will be dependent upon the size of the tophaceous mass (Figs. 6 and 8). Smaller tophi cast no shadows whatever.

The renal calculi which are encountered in gouty individuals consist largely of agglomerations of ammonium urate crystals. These uratic stones are relatively small, ranging in size from 1 to 3 or 4 mm. in diameter. Such stones are not radiopaque and, because of their small size, they do not produce filling defects which can be detected in the average urograms.

Fig. 8. An exceptionally large tophaceous mass in the region of a bunion joint.

SUMMARY

The roentgenographic changes which are encountered in patients with gout may be expected to reflect the progressive clinical and pathological features of this disease. For the proper interpretation of these roentgenographic changes, an understanding of the life history of gout and the pathologic changes associated with this condition is essential. The fundamental lesion produced in tissues by gout consists in a unique granuloma resulting from the reaction of tissues to the deposition of uratic crystals. Agglomeration, fusion, and centrifugal expansion of these tubercles bring about the destruction and disorganization of the tissues in which they are found.

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DISCUSSION

Ray A. Carter, M.D. (Los Angeles, Calif.): This is an excellent, orderly exposition of gout, and its three stages are logically presented. The two earlier stages which Drs. Rosenberg and Arens describe are the ones in which most can be done for the patient and in which we have little or no roentgen evidence. Films are requested to "rule out" gout. The negative film here, as in rheumatoid arthritis, is not an innocent thing, because a potentially crippling condition may be progressing in spite of the negative roentgenographic picture. The real roentgen evidence is predominantly of the third stage of gout, a stage of irreparable injury. Even an earlier osteoporosis which the authors displayed had definite associated hypertrophic change in the joint. A secondary osteoarthrosis occurs so frequently in these conditions that Hench has said that advanced gout may be indistinguishable from osteoarthrosis—logically enough, because secondary arthrosis is a part of the picture.

In regard to tophi and calcifications, it is true that most of them, as Dr. Rosenberg said, are not radiographically dense. Nevertheless, we do occasionally see sharp, spicular, bundle-like densities from which it is difficult to avoid assuming that considerable calcium is present, whatever its origin may be.

Gout may appear much like rheumatoid arthritis. Drs. Rosenberg and Arens have displayed a pannus, with its associated destruction of the cartilage, quite analogous to the process occurring in rheumatoid arthritis.

Again I would like to emphasize that this disease should be first diagnosed, if possible, not by the radiologist but from the clinical picture which the authors have so well described.

SUMARIO

La Gota

Es de esperar que la naturaleza de las alteraciones radiográficas observadas en los gotosos reflejen las características clínicas y patológicas evolutivas de dicha enfermedad. Para la debida interpretación de esas alteraciones radiográficas resulta indispensable conocer la biología de la gota y las alteraciones patológicas vinculadas con dicho estado. La lesión fundamental producida en los tejidos por la gota consiste en un granuloma único en su género y proveniente de la reacción de los tejidos a los depósitos de cristales uráticos. La aglomeración, fusión y expansión centrífuga de esos tubérculos ocasionan la destrucción y desorganización de los tejidos afectados.

The Roentgenologic Diagnosis of Appendiceal Calculi[1]

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THE OCCURRENCE of calculi in the appendix has been familiar to surgeons and pathologists for many years, but there is no record of a correct preoperative diagnosis of this condition prior to the use of x-rays. The importance of early diagnosis at once becomes apparent when it is realized that appendiceal calculi usually result in acute appendicitis and that the incidence of perforation in these cases is about 50 per cent.

Weisflog (63), in 1906, contributed the first case report with a correct preoperative diagnosis, demonstrating two calculi in the region of the appendix on a roentgenogram. In a study of 100 cases reported since that time, we have been able to find only 11 more in which the diagnosis was made preoperatively and proved surgically. In an additional 11 instances surgical confirmation was lacking. In 19 patients an incorrect interpretation of the x-ray films was made, and in 13 others the preoperative diagnosis was not clearly stated. In the remainder roentgen studies were not made. In spite of these figures, we believe that the roentgen diagnosis is usually easy to make.

Between June 1943 and June 1946 we encountered 10 patients with appendiceal calculi. Nine of these had roentgen studies from which a diagnosis was made, and 7 of these cases were surgically verified. One patient had no roentgenologic examination, and the diagnosis was first made at operation. During this period, an estimated 300 appendectomies were performed in the various hospitals in which these patients were seen.

This paper is based on 100 cases reported in the literature and the 10 cases from our personal experience, brief histories of which follow.

REVIEW OF CASES

CASE 1: *Acute appendicitis with perforation eight hours after onset; stone in appendix diagnosed radiologically; surgical confirmation; death from acute generalized peritonitis.*

C. L., a white male, age 19, was admitted on July 7, 1943, with the history of abdominal pain for eight hours, associated with vomiting. There had been no previous attacks. The temperature was 101° F. Examination was negative except for diffuse rigidity and tenderness in the abdomen, more marked in the right lower quadrant.

Flat and upright films of the abdomen (Fig. 1, A), made to rule out perforated peptic ulcer, showed no free air under the diaphragm, but a large, sharply defined, round, laminated, non-faceted calculus measuring 1.5 cm. in diameter was found lying lateral to the right sacroiliac joint. Stereoscopic views showed the stone in the same plane as the gas-filled cecum. A diagnosis of appendiceal stone was made.

The abdomen was explored through a McBurney incision and a perforated appendix with acute generalized peritonitis was found.

Pathologic study of the surgical specimen showed a greatly swollen, acutely inflamed appendix with a bulbous distal half. A perforation was present in the distal third. At this level a hard round stone 1.5 cm. in diameter was found (Fig. 2, A). It was brown in color and presented two small, somewhat pointed spicules on its surface. Cut sections showed a soft matrix surrounded by concentric laminations. Microscopically there was acute diffuse inflammation of the appendix. Cultures showed *E. coli* and nonhemolytic staphylococci. Chemical analysis of the dried stone showed 19 per cent calcium, 13 per cent phosphorus and 14 per cent coprosterol.

The postoperative course was very stormy. The signs of peritonitis persisted, and death occurred on the tenth postoperative day. Autopsy revealed generalized peritonitis, intestinal obstruction due to fibrinous adhesions, two perforations in the distended small bowel, and bilateral lower lobe atelectasis.

CASE 2: *Obscure acute intra-abdominal syndrome; roentgen diagnosis of stone in retrocecal appendix; perforated appendix containing stone found at operation.*

J. W., a 21-year-old white male, was admitted July 28, 1943, with dull aching pain in the mid-

[1] Accepted for publication in December 1946.
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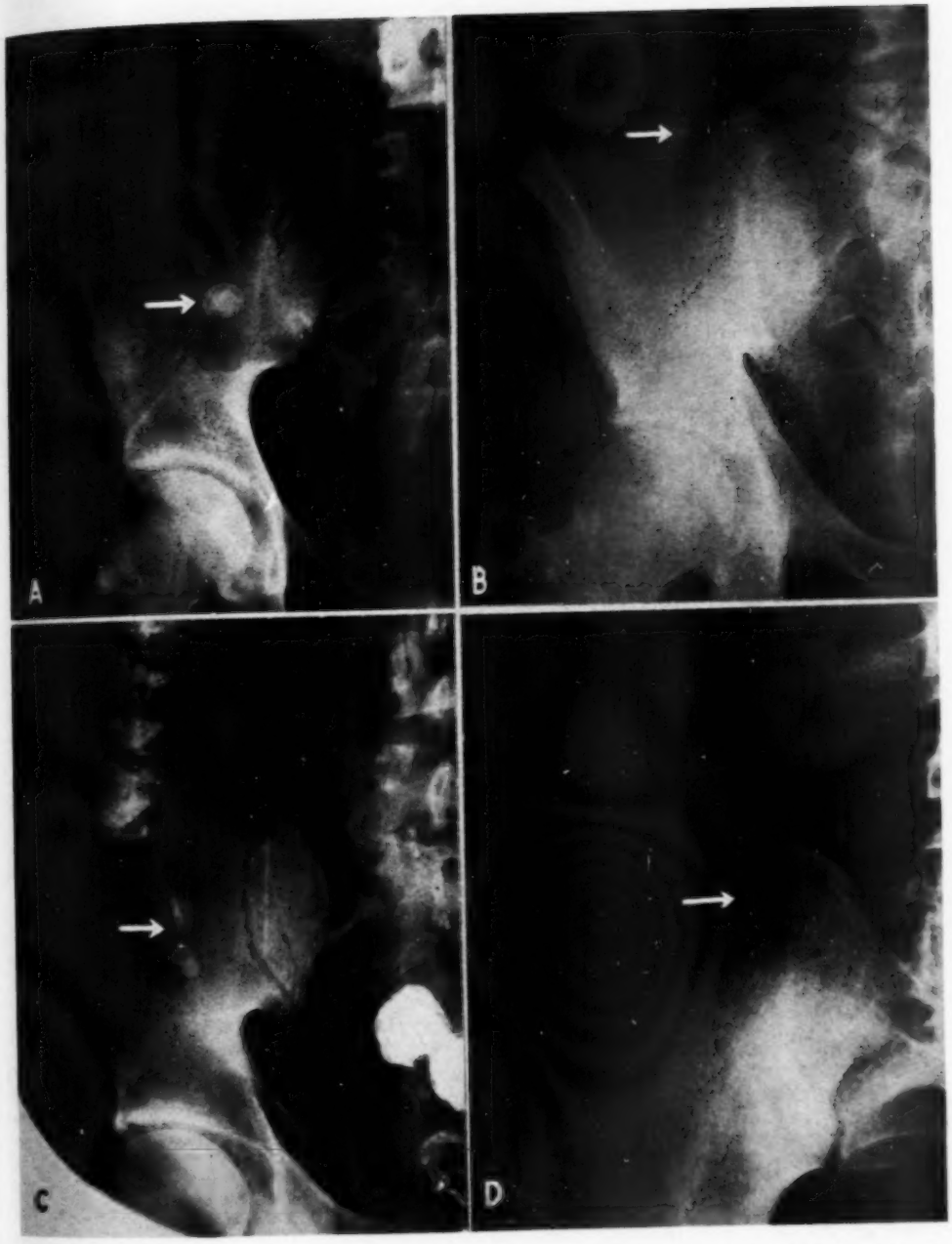

Fig. 1. Anteroposterior roentgenograms of right lower quadrant showing appendiceal calculi (arrows). A. Case 1. B. Case 2. C. Case 3, showing three calculi lying inferior and medial to the barium-filled cecum. D. Case 4. In A, B, and D, the reproductions do not show the gas-outlined cecum seen on the original films.

abdomen since the day before, gradually increasing in severity and extending toward the right side. There had been no nausea or vomiting and no symptoms related to the urinary tract. There was no history of previous attacks. The temperature was 100.8° F. Examination was negative except for slight rigidity in the right abdomen with diffuse tenderness over both lower quadrants, more marked on the right. Tenderness was also present in the right costovertebral angle. The white blood cell count was 10,150. Clinical diagnosis was obscure and exploration did not seem warranted because there was no definite localization of symptoms and physical findings. A plain film of the abdomen (Fig. 1, B) showed a very faint laminated density, about 4 mm. in diameter, in the right lower quadrant. Stereoscopic studies showed this density to lie somewhat anterior to the ilium. Immediately anterior to the calculus and extending caudally, a small amount of gas seemed to outline the cecum. The diagnosis of appendiceal calculus was made and, because of the relation between the stone and cecum, a retrocecal appendix was thought to be present.

The abdomen was immediately explored through a McBurney incision. A perforated retrocecal appendix was found. A small amount of yellow cloudy fluid was present in the area, but the surrounding structures appeared normal. The postoperative course was uneventful.

Pathologic examination showed a red, edematous appendix, the serosal surface of which was covered with fibrinopurulent exudate. A perforation was found 1 cm. from its tip. There were four calculi present (Fig. 2, B). These were soft, smooth, laminated and oval, all lying in the immediate vicinity of the perforation. The largest measured 1 × 0.6 × 0.6 cm. and the smallest 0.6 × 0.3 × 0.2 cm. None of the stones was faceted. Microscopically the appendix showed diffuse infiltration of inflammatory cells with some evidence of fibrous changes, and a pathological diagnosis of acute recurrent appendicitis was made. Cultures showed *E. coli*. Chemical analysis of the dried stones showed 21 per cent calcium, 10 per cent phosphorus, and 10 per cent coprosterol.

CASE 3: *Acute appendicitis with abscess formation and multiple stones in appendix; correctly diagnosed from clinical and x-ray findings; surgical confirmation.*

W. J. S., a 29-year-old white male, was admitted on June 22, 1943, complaining of headache and generalized aching for three days, and nausea, vomiting, and diarrhea for one day. There was a slight dysuria, but no abdominal pain. The patient had had no previous attacks. The temperature was 103° F. Examination was essentially negative except for slight distention and resistance across the lower abdomen with generalized abdominal tenderness. Rectal examination was negative. The white blood cell count was 13,850 and the urine contained 20 to 30 white blood cells per high-power field. The stool showed a 4+ test for occult blood. Stool cultures were later reported positive for salmonella organisms, probably of the enteritides group. Sigmoidoscopy showed a red edematous mucosa with many petechial hemorrhages.

Because of the gastro-intestinal symptoms and findings, a barium enema study was done on June 24. It showed localized irritability and spasticity in the sigmoid and slight irritability in the cecum. A density seen medial to the cecum was thought to represent the barium-filled terminal ileum.

The following morning, pain developed in the abdomen, more localized in the right lower quadrant, and a definite tender mass was discovered in that region. Appendiceal abscess was suspected and it was decided to wait for better localization before surgical intervention. In the meantime, one of us (B. F.), recalling the density medial to the cecum, requested that the patient be again examined roentgenographically. Re-examination (Fig. 1, C) showed the shadow in question to be composed actually of three sharply defined laminated densities; on lateral and stereoscopic anteroposterior views these were shown to be in the same plane as the cecum, which still contained barium. They did not present a faceted appearance. A diagnosis of appendiceal stones was made.

Since the patient seemed to be tolerating the infection poorly, exploration through a right rectus incision was performed on June 25. Marked injection and fibrinopurulent exudate were found, localized to the right lower quadrant. The appendix appeared swollen and injected. A small perforation was present about 6 mm. from the attachment to the cecum. A stone protruded through this perforation. The postoperative course was complicated by a wound infection and by a pelvic abscess, but the patient eventually recovered.

Pathologic examination showed an acutely inflamed appendix 9 cm. long, the proximal diameter measuring 2 cm. and the distal, 0.8 cm. There were five smooth, oval, hard, dark brown stones present (Fig. 2, C). The largest measured 1.5 × 1.0 × 0.5 cm. and protruded through the perforation; the smallest measured 0.2 cm. in diameter. All the stones were laminated but only the four smaller ones were faceted. The cut surfaces were dark brown, somewhat soft, and friable. An acute suppurative appendicitis was found on microscopic examination. Chemical analysis of the dried stones showed 21 per cent calcium, 11 per cent phosphorus, and 8 per cent coprosterol.

CASE 4: *Suspected acute appendicitis; stone diagnosed on roentgen examination; surgical confirmation.*

R. B., a 20-year-old white male, was admitted June 30, 1943, with a history of dull aching right lower quadrant pain for two days, associated with nausea. There was no history of previous attacks.

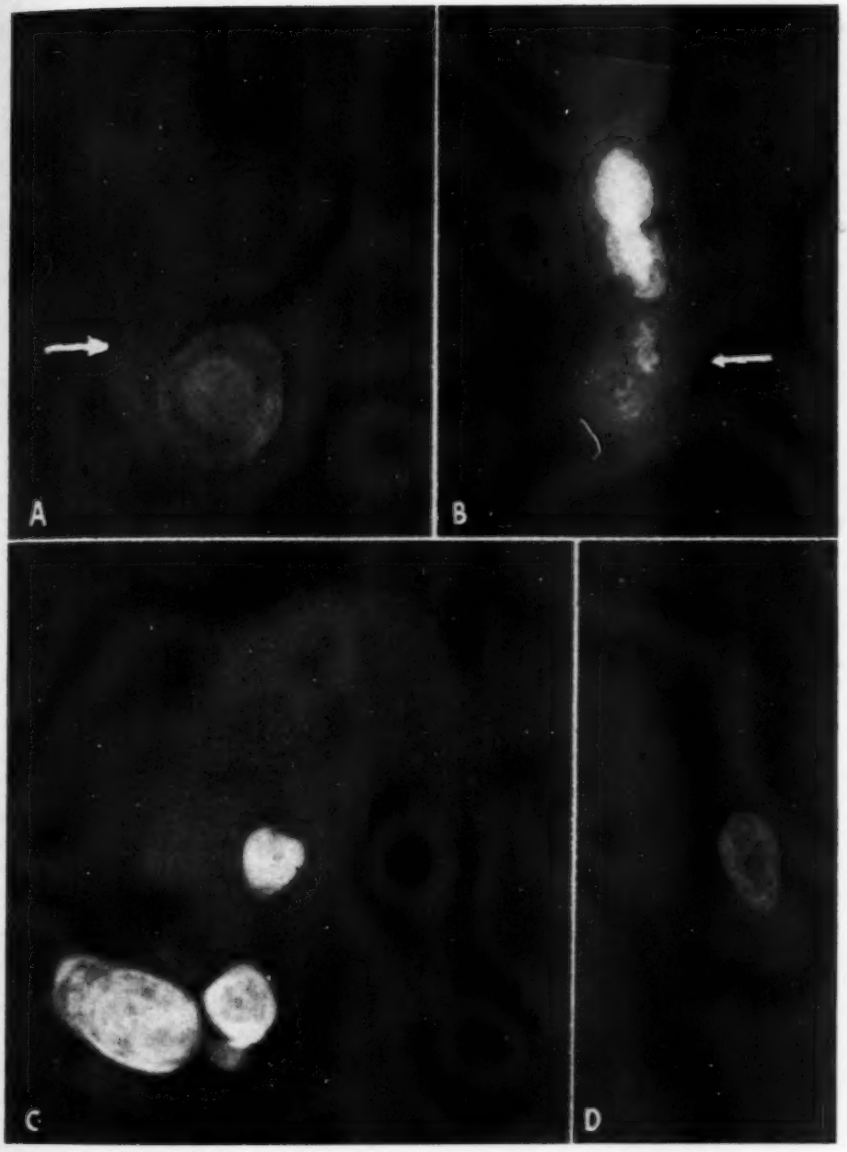

Fig. 2. Roentgenograms of appendices removed at operation, showing appendiceal calculi *in situ*.

A. Case 1. Solitary laminated calculus in distal end of greatly swollen appendix. Arrow points to site of perforation.

B. Case 2. Four laminated calculi in distal two-thirds of swollen appendix. Arrow points to site of perforation.

C. Case 3. Five laminated and faceted calculi in the proximal third of a swollen appendix. The largest stone protrudes through the perforation. Note lesser involvement of the distal appendix.

D. Case 4. Laminated calculus in distal end of normal-sized appendix. No perforation.

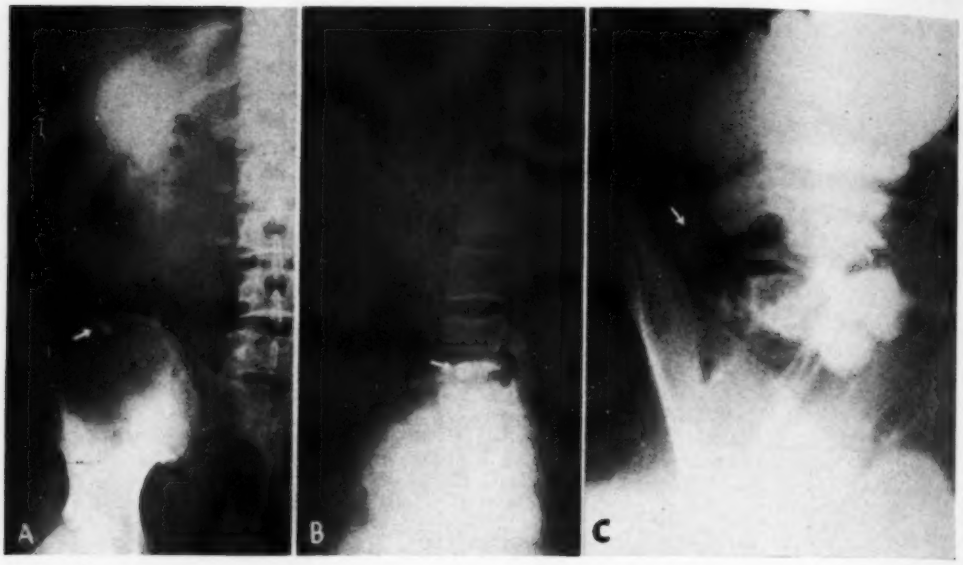

Fig. 3. Case 5. Perforated appendix with drainage and appendectomy (?) nineteen years before. A. Antero-posterior view. B. Right lateral view. C. Oblique view, following barium enema. Calculus (arrows) lies posteriorly and closely related to cecum.

The temperature was 97.8° F. Physical examination was negative except for tenderness and slight resistance in the right lower quadrant, and right costovertebral angle tenderness. Rectal examination was negative. The white blood cell count was 8,250 and the urine was normal. Acute appendicitis was suspected. A KUB film of the abdomen (Fig. 1, D), made because of the costovertebral angle tenderness, showed a faint, well defined oval density below the level of the crest of the right ilium. It was not faceted. Stereoscopic studies showed the position to be just behind the plane of the cecum, which was outlined by gas and extended about 6 cm. below the calculus. It was concluded that an appendiceal stone was present, and from the relation of the stone to the cecum, the appendix was believed to be extending cephalad, in a retrocecal position.

The abdomen was explored through a McBurney incision and the appendix was found to be bound down to the posterior wall of the cecum, pointing upward toward the hepatic flexure.

On pathologic examination the appendix showed a moderate congestion of the serosa. A hard, laminated, non-faceted, dark brown, oval stone measuring 5 × 7 mm. was found in the tip (Fig. 2, D). The wall of the appendix was thinner in the region of the calculus than elsewhere. The stone presented a hollow center. Microscopically, the acute reaction was greatest in the region of the stone. In the proximal part of the appendix no inflammatory changes were noted. Some fibrous changes were also observed, and a pathologic diagnosis of acute recurrent appendicitis was made. The patient recovered without any complications.

CASE 5: *Perforated appendix 19 years ago with postoperative draining sinus; no recent symptoms; stone in region of appendix on x-ray film; no surgery.*

K. H., a white male, aged 27, was referred for a gastro-intestinal series prior to induction into the Army, because of the history of surgical drainage of a perforated appendix nineteen years earlier. At that time an appendectomy was supposed to have been performed, but no operative note was found in the hospital record. The wound drained for about six months after the operation and ultimately healed. A roentgenogram of the abdomen at that time was reported negative for foreign body. In the interval there had been few symptoms related to the abdomen. Physical examination was entirely negative except for an extensive scarred area in the right lower quadrant.

A plain film of the abdomen (Fig. 3, A) preceding the gastro-intestinal series showed a sharply defined, laminated, oval, non-faceted shadow, 1.5 × 1.0 cm., in the right lower quadrant at about the level of the iliac crest. Two small spicules projected from its inferior margin. A lateral view (Fig. 3, B) showed the density to lie posteriorly. On barium enema study (Fig. 3, C), the stone appeared closely related to the posterior wall of the cecum. Both cecum and stone were completely fixed to palpation on fluoroscopic examination.

From the history and roentgenologic findings, it is believed that the appendix may not have been re-

moved at the original operation and contained a calculus, or that one subsequently developed. Another possibility is that the stone was expelled into the peritoneal cavity when the appendix perforated and was present but not recognized on the subsequent roentgenogram of the abdomen.

CASE 6: *Appendiceal calculus an incidental finding on roentgenographic examination; surgery not performed.*

D. J. J., a 25-year-old colored soldier, was referred for roentgenograms of the lumbar spine on Oct. 16, 1943, prior to his discharge from the Army. He had had a backache following calisthenics three weeks before. The severe pain lasted only one day, but there was a slight persistent aching until a few days before the x-ray examination, when the pain disappeared completely. No other symptoms were noted. There had never been abdominal distress of any kind. Examination was entirely negative except for slight well localized tenderness in the right lower quadrant and slight rectal tenderness on the right.

On the anteroposterior view of the lumbar spine a calcification was found in the right lower quadrant, and further studies, including a barium enema examination (Fig. 4), showed it to be a sharply defined, laminated, non-faceted stone constantly related to the medial aspect of the cecum. It was extremely mobile, especially with respiration. It measured 1.5 × 2 cm. The appendix did not fill with barium.

The patient was discharged from the Army because of an unrelated condition and arrangements were made for his future medical care.

CASE 7: *Acute appendicitis; calculus in line of right ureter on roentgenogram; urinary stone ruled out by intravenous pyelography; x-ray diagnosis of appendiceal calculus confirmed at operation.*

J. B., white male, aged 19, was admitted Nov. 11, 1943, complaining of headache and gradual development of epigastric distress, which later shifted to the right lower quadrant. Nausea began after admission and he vomited once. No urinary symptoms were evident. There had been a similar attack about one year earlier, lasting for two days. The temperature was 98.6° F. Physical examination was negative except for tenderness and slight abdominal rigidity in the epigastrium and right lower quadrant. The rectal examination showed tenderness on the right. The urine revealed a heavy trace of albumin with 8 to 10 red blood cells and 20 to 30 white cells per high-power field, with occasional white cell clumping. The white blood count was 16,000, with 52 per cent polymorphonuclears and 46 per cent lymphocytes.

A roentgenogram of the abdomen (Fig. 5, A) was made because of the urinary findings and showed a sharply defined laminated calculus in the line of the lower right ureter. An intravenous pyelogram to rule out a ureteral calculus showed the calcification lying medial to the right ureter. A diagnosis of appendiceal calculus was made.

Fig. 4. Case 6. Anteroposterior spot film of right lower quadrant following barium enema, showing laminated calculus (arrow) adjacent to medial surface of cecum. No operation.

Appendectomy showed an acutely inflamed nonperforated appendix, which lay inferior and medial to the cecum.

Pathologic examination showed a markedly congested serosa covered with fibrinopurulent exudate. A single, hard, laminated, oval calculus (Fig. 5, B), 1 × 0.6 × 0.6 cm., was found in the proximal third of the appendix. It was not faceted. Microscopic examination showed a diffuse acute appendicitis. Recovery was uneventful.

CASE 8: *Obscure abdominal symptoms and backache; roentgenologic diagnosis of calculus in retrocecal appendix; surgical confirmation; complete relief of symptoms.*

A white soldier, aged 39, was admitted to a field hospital June 15, 1945, because of low back pain. Since June 1944 he had had three attacks of pain in the epigastrium and one attack of lower right quadrant pain. These attacks lasted for two to fourteen days each and were associated with vomiting. Between attacks and on admission there was constant vague epigastric distress, worse after meals, with occasional vomiting. The back pain began about one month before admission and was fairly constant and of varying severity. It was not related to exercise or position.

On admission to the field hospital, the physical examination was completely negative. There was no abdominal tenderness. The temperature was

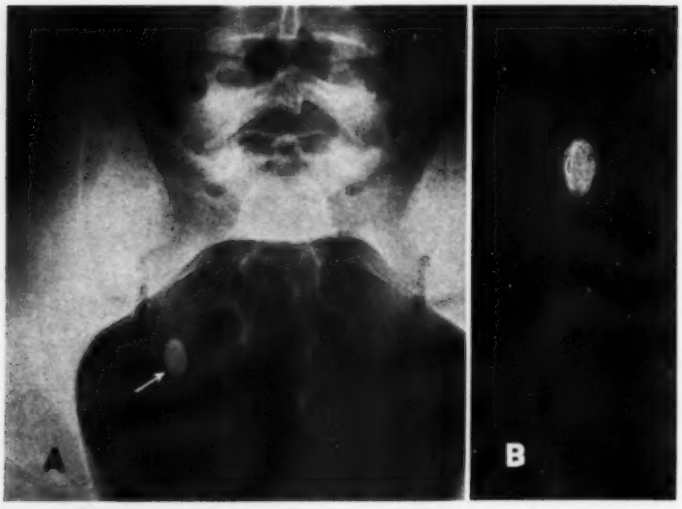

Fig. 5. Case 7. A. Anteroposterior view of the pelvis shows a laminated calculus (arrow) in the line of the right lower ureter. An intravenous pyelogram showed the calculus medial to the ureter. B. Roentgenogram of the appendix after removal, showing the calculus in the proximal third of the slightly swollen organ. No perforation.

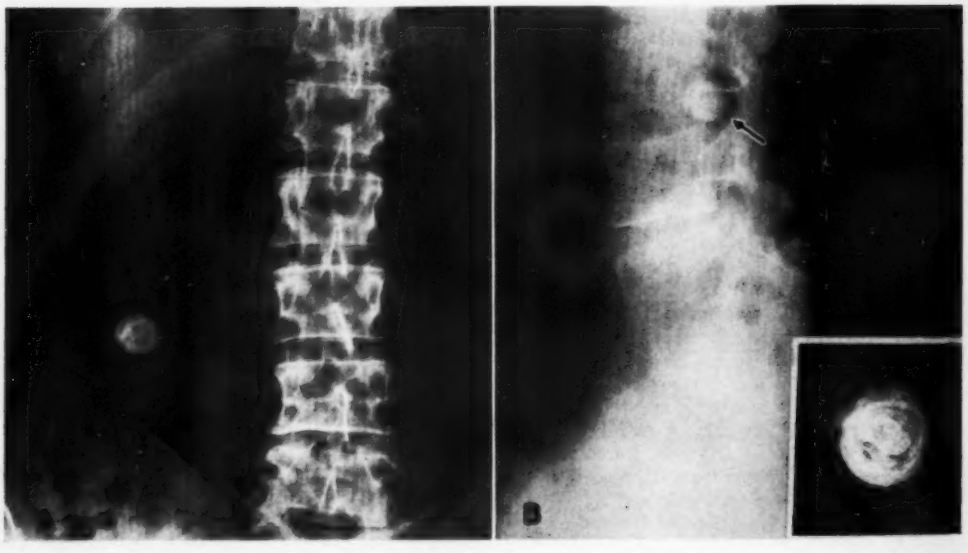

Fig. 6. Case 8. A. Anteroposterior view of abdomen showing laminated calculus above right iliac crest. B. Lateral view showing calculus (arrow) lying far posteriorly in abdomen. Inset: Roentgenogram of calculus showing laminations.

normal. Roentgenograms of the lumbar spine were negative except for a round laminated calcification, 1.75 cm. in diameter, in the posterior portion of the right lower quadrant, 3 cm. above the iliac crest. A gallbladder series showed a normal functioning gallbladder lying well above the calculus. Following a laxative, moderate abdominal pain developed, the temperature rose to 99.6°, and there was mild lower abdominal tenderness. These symptoms subsided after thirty-six hours.

The patient was transferred to a general hospital for further study. On admission he still complained

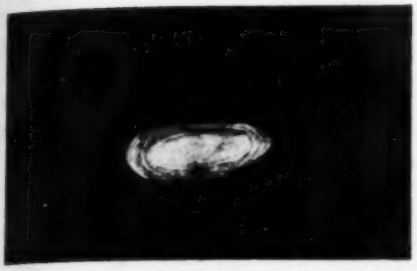

Fig. 7. Case 9. Roentgenogram of laminated calculus found in appendiceal abscess.

of epigastric distress and mid-line back pain. His white cell count was normal, but his temperature occasionally rose to 99.4°. A clinical diagnosis could not be made, although duodenal ulcer was suspected. On reviewing the films (Fig. 6), a diagnosis of appendiceal calculus was thought likely. In the absence of fever and leukocytosis, it was considered safe to do a barium enema study. This showed the calculus closely related to the posteromedial wall of the cecum. It moved slightly with respiration but was immobile to palpation. Over it there was slight tenderness to pressure. A diagnosis of a calculus in a retrocecal appendix was made.

At operation the appendix was found adherent to the posterior wall of the cecum, the tip pointing upward. The cecum maintained a relatively high position. The appendix was removed with difficulty. It was 4 cm. long. About 0.5 cm. distal to its cecal attachment was a large circular swelling. Distal to this swelling the appendix narrowed abruptly.

On opening the appendix, a large smooth, brownish-green spherical calculus was found (Fig. 6, inset). It measured 1.5 cm. in diameter. On section it showed concentric laminations. Proximal to the stone the mucosa of the appendix was normal. In the dilated portion of the appendix the mucosa presented a granular, injected appearance. Distal to the stone the mucosa appeared normal. Microscopic sections showed moderate acute appendicitis.

The postoperative course was uneventful and all the symptoms disappeared. One month later the patient was discharged to duty.

CASE 9: *Clinical diagnosis of appendiceal abscess; no roentgenograms; operation showed ruptured appendix with calculus in abscess cavity.*

G. S., a 20-year-old German prisoner-of-war, was admitted July 21, 1945, with a history of diarrhea for three weeks, followed by generalized abdominal pain which subsequently localized in the right lower quadrant and persisted. He had had vague abdominal pain for some time preceding this attack. Examination on admission revealed no spasm or rigidity, but a tender mass was felt in the right lower quadrant. Urine was negative; the white blood

Fig. 8. Case 10. Anteroposterior view of abdomen showing laminated calculus (arrow). Inset: Roentgenogram of appendix after removal, showing three laminated calculi.

count was 10,500 and the sedimentation rate was 32. No roentgenograms were made.

The appendix was not found at operation, but there was a small hole in the base of the cecum. An appendiceal abscess, containing 3 c.c. of pus and a calculus, was present. The calculus was nonfaceted, firm, dark brown, cylindrical in shape, and measured 1.2 × 0.4 × 0.4 cm. Its cut surface was laminated (Fig. 7).

The patient made an uneventful recovery.

CASE 10: *Clinical diagnosis of ureteral stone; roentgen diagnosis of calculus in retrocecal appendix; acute retrocecal appendicitis with calculi found at operation.*

R. L., a 24-year-old white male, was admitted to the Cincinnati General Hospital on Aug. 20, 1946, because of severe constant right flank and right lower quadrant pain beginning seven hours before admission. Pain was accompanied by nausea and one liquid stool.

For the past three years the patient had suffered intermittent bouts of mild abdominal pain lasting up to fifteen minutes, usually periumbilical and in the right lower quadrant, not associated with nausea or vomiting. During the week preceding admission

these attacks occurred almost daily, and during this period urgency with nocturia developed.

On admission the temperature was 100° F. There was tenderness to the right of the umbilicus and in the right flank, with rebound tenderness referred to the right lower quadrant.

The white blood cell count was 11,500 and the urine showed 3 to 5 red blood cells per high-power field. Because a right ureteral calculus was suspected, a KUB film of the abdomen was obtained (Fig. 8). This showed a laminated calcification measuring 6 × 9 mm. lying at the level of the right iliac crest, somewhat laterally. Lateral and stereoscopic anteroposterior views showed the calculus lying just posterior to the ascending colon, about 3 inches above the lower end of the gas-filled cecum. A diagnosis of calculus in the tip of a retrocecal appendix was made.

The patient was immediately explored through a McBurney incision and an acutely inflamed retrocecal appendix closely adherent to the postcecal wall was found. The tip pointed upward toward the hepatic flexure. Appendectomy was performed with some difficulty.

Pathologic study of the surgical specimen showed an acutely inflamed appendix. The distal end was bulbous and covered with fibrin. No perforation was found. The appendix was 5.5 cm. in length, 0.7 cm. in diameter at the proximal end, and 1.7 cm. in diameter at its distal end. It contained about 2 c.c. of thick dark brown pus with a fecal odor, and three laminated soft brown calculi (Fig. 8, inset), having the consistency of putty. The largest of these, the only one shown on the KUB film, lay in the bulbous tip and measured 1.3 × 0 6 × 0 6 cm. The center of each calculus was quite soft. The mucosa of the appendix showed small granulations.

The postoperative course was uneventful. The patient has been symptom-free since the operation.

DISCUSSION

Much confusion has arisen in the literature because of the terms ordinarily used to describe appendiceal calculi. They have been variously called fecaliths, stercoliths, coproliths, concretions, enteroliths, stones, and calculi. The first four terms have been applied also, by many authors (21), to the non-calcified inspissated fecal masses so commonly found in the appendix. These are not included in the subject under discussion. The term *enterolith* implies that the stone has developed in the intestine and is identical with the rare calcified intestinal calculus reported under that name (49). This is not the case, as we shall see later. The term *appendiceal calculus* seems preferable to us, since it implies appendiceal origin of a calcified mass.

Incidence: Bunch and Adcock (7) state that they have encountered only one case of appendiceal stone in over 2,000 patients with appendicitis. Golden (21) remarks that "fecal concretions which contain enough calcium to cast an x-ray shadow must be quite uncommon in this country. I can't remember having seen one." Yet Steinert *et al.* (57) found 10 examples among 104 appendectomies. There have been slightly over a hundred cases reported since 1900, the majority in the foreign literature.

Etiology: There is some difference of opinion regarding the etiology of appendiceal calculi, but most authors now agree that they are generally formed, at least in part, *in situ*. This point of view is supported by the following evidence:

(1) The majority of stones, being more than 1 cm. in diameter, are too large to pass through the cecal orifice of the appendix. Experimentally Guinard (quoted by Calzolari, 8) was unable to force a foreign body the size of a cherry seed into the appendix.

(2) Kelly and Hurdon (31) report a case in which three small stones were found completely embedded in the appendiceal wall and a larger stone was anchored in the wall by a pointed fang-like process. They quote Ribbert as describing microscopically a continuity between the mucus in the outer layer of a stone and the mucous glands in the appendix.

(3) The chemical composition of appendiceal stones differs greatly from that of gallstones or true enteroliths.

(4) Foreign bodies which lodge in the appendix often become encrusted with calcareous material and may even form the nucleus of a typical calculus (41).

The most plausible and widely accepted explanation of the origin and development of appendiceal stones is that offered by Kelly and Hurdon (31). They state that if the normal return of the fecal contents from the appendix to the cecum by peristalsis is impaired in any way, inspissation of varying degree occurs. The combination of irritation from the fecal mass and bacterial activity produces a low-grade catarrhal inflammation with its attendant secretion of mucus. Inorganic salts contained in the mucus are precipitated (probably by bacterial action) on the surface of the dried fecal particle, which thus increases in size. The repetition of this process results in the lamination almost constantly present. Eventually, if some complication does not intervene, the enlarging stone produces pressure atrophy in the secretory glands of the appendix and its growth ceases.

The chemical and microscopic structure of the calculi appears to lend support to this theory. The presence of vegetable fibers in the stones analyzed indicates that fecal material is present (40). Tests for mucus are positive (31). Large masses of bacteria are constantly present.

The next question which arises is the relationship between appendiceal stones and acute appendicitis. From a statistical standpoint there can be little doubt that such a relationship exists. In the entire series of 110 cases, only 5 failed to present clinical or surgical findings of acute appendicitis. The high incidence of perforation also supports this premise.

We believe that in the presence of an appendiceal calculus, obstruction is more complete and distention more marked than in simple acute appendicitis. Consequently perforation is more likely to occur. To support this point of view, we found that in every case in which the relative locations were recorded, the perforation always occurred at or distal to the level of the stone. It is possible that the stone itself erodes through the wall of the inflamed appendix, but from the available evidence this is probably uncommon.

Other less common sources of appendiceal stones have been described. A few instances of typical gallstones containing large amounts of cholesterol, bile salts, and pigment have been reported (31). A foreign body may sometimes form the nucleus of a stone (39, 41). Unaltered foreign bodies in the appendix are not uncommon, but this subject is beyond the scope of our paper. Two instances of pure bismuth stones in the appendix, long after a gastro-intestinal series, have been reported (39, 43).

Clinical Findings: Of 60 patients whose sex was stated, 47 were males and 13 females. This preponderance of males conforms to the sex ratio observed in acute appendicitis. The largest number of patients, 21, were in the third decade of life, as compared to 12 in the second and 15 in the fourth.

There are no characteristic symptoms or physical findings which might lead to the diagnosis of appendiceal stone. The diagnosis depends entirely on the roentgen findings. A rather frequent occurrence of urinary symptoms has been reported (39). Recurrent attacks were present in 32 of 52 patients in whom this point was mentioned.

It has been stated (44) that perforation occurs quite early in the course of this disease. In our Case 1, perforation occurred within eight hours, and in Case 2 within twenty-four hours of the onset of symptoms. In the case reports in the literature, the time interval between onset and perforation was seldom clearly stated.

Only 5 patients had no symptoms related to the appendix. In 2 others, stones were present as incidental findings on a previous film, but subsequently acute appendicitis, developed in both, in one with perforation (32, 55).

Roentgenologic Diagnosis: When a stone has been demonstrated on a plain film, a variety of procedures have been recommended to localize it. When appendiceal calculus is suspected in acute cases, it has been our policy to obtain immediately lateral and stereoscopic anteroposterior views of the area. These films are viewed wet,

since perforation, if it has not already occurred, must be considered imminent. The true diagnosis was not suspected in Case 3, and a barium enema was given. We believe the use of a barium enema is inadvisable in acute appendicitis. In 4 of our cases we were able to determine correctly the relationship between the calculi and the gas-filled cecum on stereoscopic films without a contrast medium.

Where the symptoms are not acute, the patient is studied more thoroughly. Genito-urinary, gallbladder, colon and gastrointestinal studies are also made.

Because of the variations in the anatomic position of the appendix, the shadow of the calculus may be found anywhere in the right abdomen, and rarely even on the left side. In all but 5 cases in the literature the stone was in the right lower quadrant, usually at the level of the sacroiliac joint or iliac crest. Twice it was in the right upper quadrant and mistaken for a gallstone. In one patient it was found in the left lower quadrant and correctly diagnosed (16). In a number of instances it was found in the region of the lower right ureter (Case 7), so that pyelography was indicated.

Lamination was demonstrable in nearly all of the patients in whom the x-ray appearance of the calculus was completely described. This finding is of great importance as a diagnostic criterion, since a laminated calculus in the lower right quadrant will almost invariably prove to be an appendiceal stone.

A sharp regular outline was present in practically all the cases. The presence of facets is not uncommon, especially when the stones are multiple, but the demonstration of facets on the roentgenogram is usually difficult.

Of 16 patients to whom barium was administered orally or by enema, 8 showed partial appendiceal filling.

Study of the mobility of the density on fluoroscopic palpation is not very helpful in diagnosis. In 15 patients studied for this finding, 8 showed appreciable mobility while in 7 there was partial or complete fixation. In Case 6, which was without clinical symptoms, the respiratory excursion of the calculus was quite marked.

When multiple calculi are present, some of the smaller ones may not be visualized on the preoperative films (Cases 2 and 10).

The value of routine roentgenography in acute abdominal conditions receives further support from this study, since this procedure was the chief factor in reaching a correct diagnosis in at least 4 of our 8 cases, permitting a correct and prompt surgical approach.

Differential Diagnosis: (1) *Urinary Calculi.* In 10 of the 18 cases incorrectly diagnosed by x-ray examination, the stones were interpreted as urinary calculi. The posteromedial location of the calculi and the absence of lamination favor ureteral calculus. Pyelography may be indicated in the more confusing cases (Case 7).

(2) *Calcified intra-abdominal lymph nodes* are sometimes quite confusing but the wide range of mobility, the dentate borders, the irregular shape, and granular structure of these densities are usually diagnostic.

(3) *Gallstones.* Occasionally, difficulty might arise because of a low-lying gallbladder or high position of the cecum and appendix. Although the x-ray appearance of the two types of stones is often identical, differentiation is usually easy if the cecum is visualized. Gallstone obstruction at the ileocecal valve following spontaneous internal biliary fistula should be readily differentiated by the presence of the symptoms and roentgenologic findings of intestinal obstruction, with perhaps gas outlining the biliary ducts.

(4) *Phleboliths* are seldom a problem because of their characteristic position and configuration, symmetrical distribution, and absence of lamination.

(5) *Foreign bodies* should give no difficulty because of their characteristic shape and density.

(6) *Non-reticulated bone islands in the ilium* are easily located on stereoscopic films.

(7) *True enteroliths in the bowel.* These very rare calculi are said to be larger and

less opaque than appendiceal calculi and surrounded by a thin layer of gas.

(8) *Calcifications in epiploic appendages, cysts, tumors, and ligaments* have been mentioned by various authors, but differentiation should not be difficult.

In a case recently studied, we suspected an appendiceal calculus because of a triangular calcification anterior to and below the right sacroiliac joint. At surgery an acute appendicitis with perforation and abscess was discovered. The calculus was not found, but a solitary calcific plaque was felt in the right common iliac artery somewhat above the region suspected. It is possible that this accounted for the shadow seen on the film.

Pathology: The involved appendix usually shows a diffuse acute appendicitis with areas of gangrene varying in severity and extent, generally more marked at the level of the stone or distal to it. Sometimes evidence of inflammation is slight or entirely lacking proximal to the stone (Case 4).

Perforation occurred in 47 of the 99 patients in whom this complication was mentioned. In 19 cases this resulted in abscess and in 10 in diffuse peritonitis. The type of complication resulting from the perforation was not stated in 18. In 14 patients a calculus either protruded through the perforation or lay adjacent to it, while in 3 the perforation had occurred distal to a calculus. In no instance was the perforation found proximal to the calculus. In 12 patients the stone was found completely outside the appendix, having escaped through the perforation. In 18 patients the relative position of the stone and the perforation was not mentioned. The stones occurred with about equal frequency in the proximal, middle, and distal portions of the appendix.

In most of the case reports, the location of the appendix and the presence of kinks, bands, etc., were not mentioned. In 5 of our cases and in 6 reported by others the appendix was in a retrocecal position, usually bound down to the post-cecal wall. This suggests an etiologic relationship; the position of the appendix may interfere with the normal return of fecal contents from the appendix to the cecum and thus initiate the sequence of events postulated by Kelly and Hurdon (31) which culminates in the production of a calculus.

TABLE I: APPENDICEAL CALCULI: ANALYSIS OF CASES

Number of Calculi	Cases
1	69 (67.6%)
2	13 (12.7%)
3 or more	20 (19.6%)
Size (average diameter)	
Less than 1 cm.	29 (41.4%)
1–2 cm.	25 (35.7%)
Over 2 cm.	16 (22.8%)
Shape	
Oval, cylindrical	28 (53.8%)
Round	19 (36.5%)
Triangular	2 (3.8%)
Irregular	3 (5.7%)
Lamination	
Present	34 (94.4%)
Absent	2 (5.5%)
Consistency	
Hard	22 (73.3%)
Soft	8 (26.6%)

Physical characteristics of the calculi are shown in Table I. Information of this type was lacking in many of the case reports. The largest number of calculi seen in one patient was 23. The largest calculus described was 2.5 cm. in diameter and weighed 13.5 gm. Faceted calculi were described in only 8 cases, in 4 of which there were multiple stones.

Attention should be called to the fact that a number of the calculi were soft in consistency, although they contained sufficient calcium to permit their visualization on the roentgenogram. They were indistinguishable, grossly, from the inspissated fecal particles found so commonly in surgically removed appendices. It is possible that some of these soft masses represent true appendiceal calculi.

Chemical Composition: Maver and Wells (40) state that the usual composition of appendiceal stones is 1/4, by weight, inorganic material, chiefly calcium phosphates; 1/5 organic residue, mostly vegetable fibers; and 1/2 substances soluble in fat solvents, chiefly soaps, coprosterol, and small amounts of cholesterol. Other authors have reported varying amounts of magnesium ammonium phosphate (64) and

calcium carbonate (7), and absence or faint traces of bile salts and pigments (3), urates (29), silica (61), and iron (64). The stones from Cases 1, 2, and 3 were chemically analyzed and showed an average of 20.3 per cent calcium, 10.3 per cent phosphorus, and 10.8 per cent coprosterol. No magnesium or iron was found, and only traces of cholesterol.

Treatment: Most authors agree that surgery should be performed as soon as the diagnosis is made (32, 59). We feel, too, that the diagnosis of appendiceal calculus is an indication for immediate surgery whether or not the patient has symptoms referable to the appendix. As previously stated, two patients in whom a symptomless calculus was demonstrated by x-ray subsequently had acute appendicitis. If acute symptoms are present, any delay in surgical intervention may have serious consequences because of the danger of perforation. Of 36 cases in which the outcome was mentioned, 4 terminated fatally and 6 had a stormy course but recovered.

SUMMARY AND CONCLUSIONS

From a series of 100 cases reported in the literature and an additional 10 cases reported here, it is concluded that the occurrence of stones in the appendix is a serious and not infrequent condition. The almost constant presence of acute appendicitis in these cases, with an incidence of perforation of nearly 50 per cent, makes the importance of early diagnosis obvious. We have been able to diagnose this condition from roentgenologic evidence in 9 patients. Seven of these were operated upon and the diagnosis was verified.

Once the diagnosis of appendiceal calculus is made, immediate surgery is indicated. The value of roentgenography in acute abdominal conditions is stressed. It is felt that in every case of laminated calcification in the right lower quadrant the diagnosis of appendiceal stone should be entertained and immediate steps be taken to confirm or disprove it.

NOTE: We are indebted to Lt. Col. F. C. Potter, M.C., Capt. L. C. Johnson, M.C., Lt. R. Solkot, Sn.C., Dr. Samuel Rapoport, and Mr. A. A. Danish for their assistance in this study.

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SUMARIO

Diagnóstico Roentgenológico de los Cálculos Apendiculares

De una serie de 100 casos comunicados en la literatura y de otros 10 casos presentados en este trabajo dedúcese que los cálculos del apéndice constituyen un estado grave y no raro. La existencia casi constante de apendicitis en estos casos, con una incidencia de casi 50 por ciento de perforaciones, pone de manifiesto la importancia del diagnóstico temprano. En 9 enfermos de la serie actual se pudo hacer el diagnóstico por los datos roentgenológicos, y 7 de ellos fueron operados, confirmándose así el diagnóstico. Al sospechar litiasis en un caso agudo, los A. A. acostumbran obtener inmediatamente vistas laterales y anteroposteriores estereoscópicas. Estas películas son estudiadas en húmedo, visto que la perforación, sino ha sobrevenido todavía, debe considerarse como inminente.

Una vez hecho el diagnóstico de cálculo apendicular, la intervención cruenta inmediata está indicada. Recálcase el valor de la radiografía en los estados agudos del abdomen. En todo caso de calcificación laminada del hipocondrio derecho hay que considerar el diagnóstico de cálculo apendicular.

Bronchiectasis: Some Medical Features Among Military Personnel[1]

MAJOR SAMUEL COHEN, M.C., A.U.S.

THE ARMY mobilization criteria for induction list bronchiectasis as disqualifying for service. Soldiers with this disease are a definite liability. Screening by chest roentgenography on induction is much more effective in the detection of pulmonary tuberculosis than of bronchiectasis, for the latter may exist in spite of a relatively negative plain roentgenogram. Bronchography is rarely done, if ever, at induction stations. Furthermore, while a careful history alone will frequently suggest a diagnosis of bronchiectasis, this, too, is not a usual part of the examination for entrance into military service.

Next to tuberculosis, bronchiectasis was the most commonly encountered chronic pulmonary infection at the hospital from which this report comes. Altogether 101 cases were definitely diagnosed by lipiodol injection during the four-year period, January 1942 to January 1946. While bronchiectasis among military personnel differs in no respect from the condition in civilians, army life subjects soldiers to physical strains and exposures which usually precipitate hospitalization more promptly for those with pre-existing disease. In this regard, it is worthy of note that in 74 patients, bronchiectasis was diagnosed during a period of hospitalization occurring within the first six months of military service. Also, judging from the past history, 88 of the 101 soldiers had bronchiectasis prior to induction. These figures constitute a definite medical challenge. They are excusable no doubt, in some degree, because of the urgent necessity for the rapid creation of a large army.

The present study afforded an opportunity to review the clinical and roentgen manifestations of bronchiectasis in age groups representing, for the most part, supposedly healthy individuals. A plea is made for the recognition of the frequency of this disease and its early diagnosis. It cannot be emphasized too strongly that the conventional textbook triad of persistent cough, copious, foul expectoration, and clubbed fingers usually represents far advanced disease. Appropriate therapy, particularly surgical, in suitable cases can be curative. The internist must assume the responsibility for the prompt diagnosis and proper disposition of the bronchiectatic patient.

CLINICAL FEATURES

All but 2 of the 101 patients constituting this series were males; 98 were white and 3 colored. Table I shows the distribution among age groups.

TABLE I: AGE DISTRIBUTION OF 101 CASES OF BRONCHIECTASIS

	Cases
Less than 20 years	16
20 to 29 years	56
30 to 39 years	24
40 to 49 years	4
50 to 59 years	1

Past Respiratory History: There is virtual unanimity of opinion that the inception of bronchiectasis can in many instances be traced to childhood. In this series, pulmonary symptoms originated within the first decade of life in 63 cases, during the second decade in 27, and in subsequent years in the few remaining cases. Many soldiers considered their symptoms as trivial. On further inquiry it was found that 83 patients dated their "trouble" from an episode of pneumonia, of whom 49 had one attack and 34 more than one. Thirty-four soldiers also gave a history of pertussis, followed in some instances by pneumonia; in 13 patients measles had

[1] From the Respiratory Diseases Section, Medical Service, Regional Hospital, Fort Bragg, North Carolina. Accepted for publication in October 1946.

been complicated by pneumonia. Pulmonary abscess was apparently the causative agent in one case and aspiration of a foreign body in another. The incidence and role of chronic sinusitis in relation to bronchiectasis could not be adequately evaluated. A history of easy susceptibility to "colds" was common.

Symptoms: The pulmonary symptoms were of varying degree. They consisted, in the majority of cases, of a mild to moderate cough, productive of 1/2 to 2 ounces daily of non-foul sputum. Fetid sputum was present intermittently in only 14 patients. The odor is supposedly due to superimposed anaerobic and fusospirochetal infection. While considerable diagnostic emphasis has been placed on this symptom, bronchiectasis should be suspected in many cases despite its absence. In recent years, bronchiectasis has achieved greater recognition as a cause of hemoptysis. The blood is derived from the rupture of submucosal varices in highly vascularized tissue. Hemoptysis was the presenting symptom on admission in 14 patients, and in 18 additional cases the history indicated its occurrence at one time or another. Chest pain, usually mild, inconstant, and non-pleuritic in character, was a complaint in 31 cases, while 40 patients stated that they had some shortness of breath on exertion.

Constitutional symptoms, such as fatigability, weakness, anorexia, some loss of weight, and occasional fever, were present in varying degree in 30 cases. Subjective manifestations always have to be carefully evaluated in soldiers. How much a superimposed psychogenic element may have entered into the production of these symptoms would be difficult to state.

Physical Signs: The pulmonary signs were not distinctive. That most commonly encountered was persistent râles either alone or in combination with dullness. This was noted in 72 cases. Given a patient with a suggestive history, the existence of the above abnormal findings increases the likelihood of bronchiectasis. Eleven other patients presented dullness alone, and in 18 no abnormal signs were noted. This, too, is significant. Breath sound changes will depend largely on associated conditions—pleurisy, fibrosis, pneumonitis. Variation in signs before and after postural drainage was noted in some instances. Clubbing of the fingers was present in 13 cases.

ROENTGEN FEATURES

Roentgenography of the chest undoubtedly is of great value, but the use of a radiopaque substance, such as iodized oil, is necessary to establish a definite diagnosis of bronchiectasis. For convenience, the pulmonary roentgen manifestations have been divided into the following groups:

Negative	7 cases
Prominent or "exaggerated" pulmonary markings	32 cases
Linear or patchy areas of infiltration	44 cases
"Shrunken lobe"	14 cases
Miscellaneous	4 cases

Pleuritic changes, usually of mild degree, were not infrequent. Less noticeable were associated emphysematous areas. Honeycombed shadows of "highlight" were not common. To revert, for emphasis, to the statement of the opening paragraph, it is seen from the above figures that a clear or relatively clear roentgenogram does not in itself preclude bronchiectasis. The clinician should not be led astray in this respect.

Information of interest and value was gained from the induction x-ray films, which were secured and reviewed in 83 cases. Parenchymal infiltration was present in 49, and prominent bronchovascular markings in 19; in 15 cases nothing of special note was seen.

Bronchography is the only method for the positive antemortem diagnosis of bronchiectasis. The character and degree of the ectasia and its pulmonary localization can thus be readily ascertained. Several methods for instillation of lipiodol have been advocated; all give good results, depending upon the skill of the operator carrying out the procedure. There

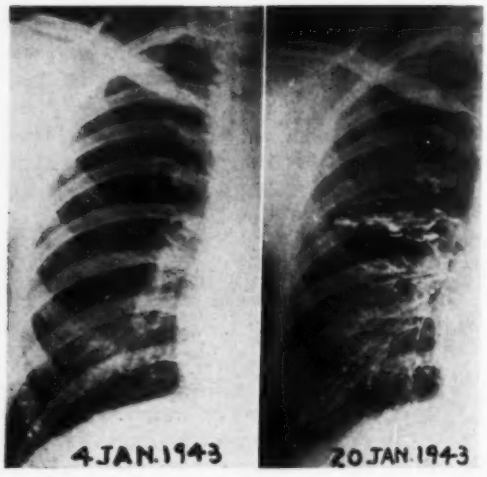

Fig. 1. Case 1: Roentgenogram, Jan. 4, 1943; bronchogram, Jan. 20, 1943.

are a few simple but practical and useful hints in bronchography which are worthy of mention: (*a*) Postural drainage before the introduction of the iodized oil is indicated in patients with moderate to copious quantities of sputum. The same procedure should be repeated in all cases immediately after roentgen films have been taken, in order to assure maximum prompt evacuation of the oil from the lungs. The likelihood of a complicating pneumonitis will thus be minimized, and obscuration and faulty interpretation of pulmonary shadows on subsequent films will be lessened. (*b*) During fluoroscopy, some of the lipiodol may perhaps be seen to have entered the stomach; if so, the prompt administration of a cathartic will eliminate the annoying symptoms of possible iodism. (*c*) In cases of recent pneumonitis, in which the possibility of underlying bronchiectasis is suspected, bronchography should be deferred until at least two weeks after the complete disappearance of the acute episode, to prevent an exacerbation. (*d*) A persistent bronchial filling defect with lipiodol is significant and may indicate organic obstruction, with possible bronchiectasis distal to the defect. (*e*) Prior to consideration of pulmonary resection, adequate visualization with oil of all five lobes is desirable. This is best accomplished in more than one sitting.

In this series, 141 lobes were involved in 101 patients. The left lower lobe was most often affected, 78 times. The diseased area not infrequently was obscured in whole or in part by the cardiac silhouette, and for

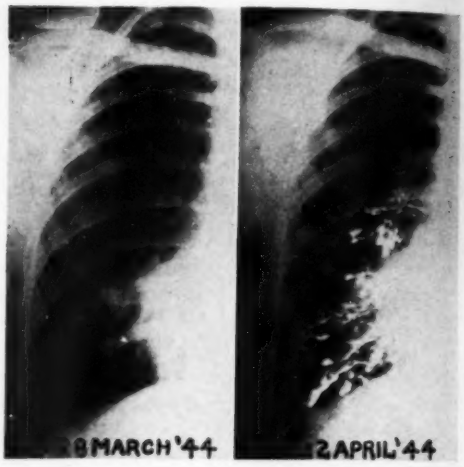

Fig. 2. Case 2: Roentgenogram, March 28, 1944; bronchogram, April 12, 1944.

TABLE II: ANATOMICAL DISTRIBUTION AND TYPE OF ECTASIA IN 101 CASES (141 LOBES INVOLVED)

	Cases
Unilobar	66
Bilobar	30
Trilobar	5
Left upper lobe	12
Left lower lobe	78
Right upper lobe	5
Right middle lobe	14
Right lower lobe	32
Cylindrical	76
Saccular	20
Mixed	45

that reason lateral or oblique x-ray films are essential. One should not overlook bronchiectasis in the lingula of the left upper lobe. Table II shows the anatomical distribution and the types of bronchiectasis encountered in this series.

Five interesting and illustrative cases have been chosen for presentation:

CASE REPORTS

CASE 1: A 33-year-old white male with six years of service was admitted to the chronic chest ward on

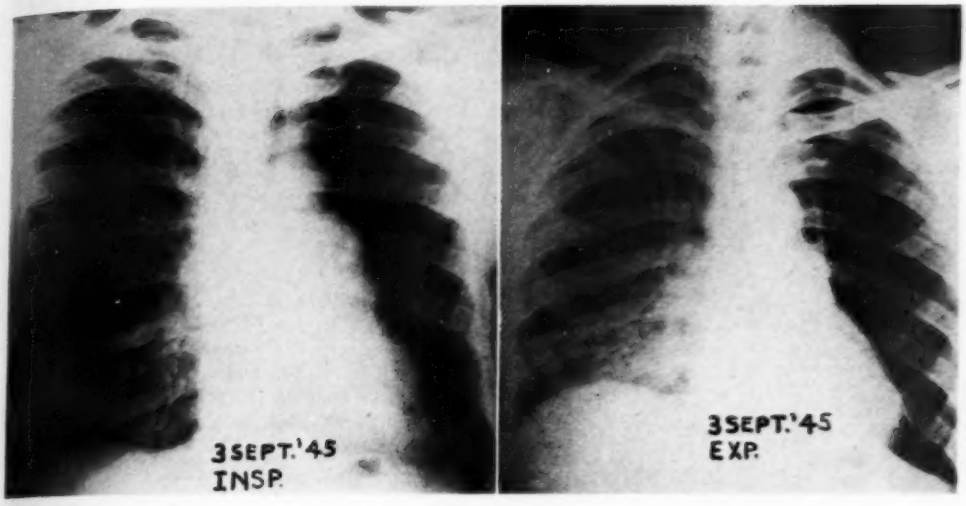

Fig. 3. Case 3: Roentgenograms made at end of inspiration and expiration, Sept. 3, 1945.

Jan. 2, 1943, with a history of three attacks of pneumonia since 1934. For the past seven years he had a cough productive of 1/2 to 1 oz. of non-foul sputum. He had a small hemoptysis in 1941 and was hospitalized elsewhere, but no definite diagnosis was made. The patient also complained of occasional mild chest pain and slight dyspnea. The right lung showed coarse râles in the second and third anterior interspaces. A roentgenogram on Jan. 4, 1943, revealed very slight linear infiltration extending outward from the right hilum where a few small "honeycombed" areas were seen (Fig. 1). Sputum examinations were negative for tubercle bacilli. A bronchogram on Jan. 20 (Fig. 1) showed definite bronchiectasis in the right upper lobe. The soldier was a valuable man in his organization and was reclassified for limited duty within the continental limits of the United States.

CASE 2: A 19-year-old white soldier with five months of military service was hospitalized March 25, 1944. He gave a history of right-sided pneumonia in 1941 with chronic cough since then, yielding about 1 oz. daily of non-foul sputum. He was somewhat dyspneic on exertion and had lost 23 lb. in weight in two months. The right lung showed dullness and râles over the middle lobe, at the base of the axilla, and posteriorly over the lower lobe. The left lung was clear. Slight clubbing of the fingers was present. An x-ray film of the chest, on March 28 (Fig. 2), showed a right-sided paracardiac density with linear infiltration along the markings in the lower lung field. The induction film showed similar findings. The bronchogram, April 12 (Fig. 2), revealed bronchiectasis of the mixed type involving the lower portion of right upper, right middle, and right lower lobe. The line of duty status was "no," and the soldier was discharged from the army.

CASE 3: A 38-year-old white male with forty-one months of service was admitted Aug. 29, 1945, because of abnormal x-ray findings observed at the separation center. The past history was most interesting. In 1911, at the age of four years, while engaged in a fight with his brother, the patient held a safety pin in his mouth, which was aspirated into the chest. Wheezing, cough, and shortness of breath developed and the boy was treated for asthma for several years. The first x-ray examination was made in 1917, when the safety pin was discovered in the left chest. In 1923, while boxing, the patient was struck on the thorax, and the following morning, he coughed up the pin.

This soldier was in an infantry division and had one year of overseas duty. He was evacuated to the United States in March 1944, because, following hospitalization for malaria, the presence of abnormal pulmonary signs and a subsequent roentgen film indicated the possibility of tuberculosis. He was in two general hospitals in this country for nine weeks. Bronchiectasis was diagnosed and he was returned to a limited duty status

On admission to this hospital the patient appeared well developed and well nourished Cough and expectoration were very slight hemoptysis had never occurred. Dyspnea on moderate exertion was the chief symptom The chest was emphysematous in contour. The right lung showed hyperresonance. Over the left lung, also, hyperresonance was marked except for an area posteriorly at the base close to the vertebral column where there was dullness with bronchovesicular to bronchial breathing and coarse râles; elsewhere the

Fig. 4. Case 3: Bronchogram, Sept. 10, 1945.

breath sounds were very diminished. There was no clubbing of the fingers. Roentgen films (Fig. 3) were obtained at the end of each phase of respiration. It was interesting to note the hyperaeration of the left lung with mediastinal shift and mediastinal pleural herniation to the left after deep inspiration, and the change in the volume and appearance of the right lung with shift of the mediastinum toward the mid-line at the end of deep expiration. The bronchogram (Fig. 4) showed bronchiectasis in the left lower lobe behind the heart. From a symptomatic point of view, the bronchiectasis was mild. Apparently, the emphysematous changes following aspiration of the foreign body were irreversible and predominant. It is somewhat remarkable that this soldier tolerated his military duties so well in the presence of this pulmonary disability.

The induction x-ray film could not be obtained. The condition undoubtedly antedated entrance into the army, and the patient was discharged *via* the separation center.

CASE 4: A white private, age 20, was inducted June 21, 1945, and admitted to the hospital Oct. 17, 1945, with a history of expectoration of blood that morning. A similar episode had occurred in 1942. The patient had pertussis followed by pneumonia in childhood. Pneumonia (right) was again diagnosed in the winter of 1941. As far back as he could remember, this soldier was subject to frequent attacks of bronchitis productive of scanty non-foul sputum. He was well nourished and developed. A few râles were present at the base of the right lower lobe posteriorly. There was no clubbing of the fingers. A roentgenogram, Oct. 18 (Fig. 5), showed slight prominence of the bronchovascular markings extending downward from the lower pole of the right hilum. A bronchogram, four days later, revealed definite bronchiectasis beneath the right diaphragmatic shadow. The history in this case was sufficient to point to the proper diagnosis. The line of duty status was "no," and the soldier was discharged.

CASE 5: The patient, a 21-year-old white soldier, entered the hospital with primary atypical pneumonia. Because of slow resolution, with persistence of cough and expectoration, bronchiectasis was suspected and confirmed by bronchography. A careful history elicited no significant respiratory tract infection in the past. There had been two previous army hospitalizations for "sore throat."

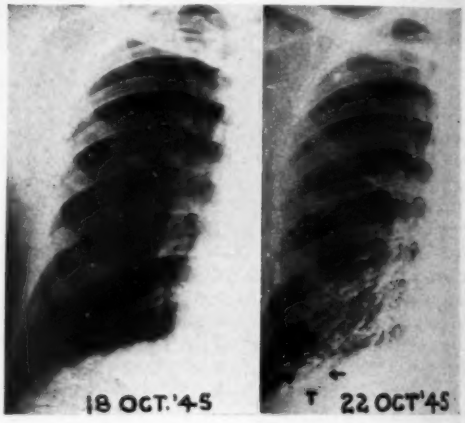

Fig. 5. Case 4: Roentgenogram, Oct. 18, 1945; bronchogram, Oct. 22, 1945, showing definite bronchiectasis beneath the right diaphragmatic shadow.

The date of induction was March 22, 1943, and the x-ray film taken at that time was later obtained and interpreted as negative. On Aug. 27, 1945, the patient had a sore throat and head cold. The following day he complained of anorexia, malaise, supraorbital headache, cough, and scanty expectoration. He visited the dispensary and obtained temporary relief. Subsequently, however, the symptoms became aggravated and on admission, Sept. 3, 1945, the patient was acutely ill, cyanotic, dyspneic and febrile (103.8°). The leukocyte count was 9,300, with 68 per cent polymorphonuclear leukocytes. A chest x-ray film (Fig. 6) taken the same day revealed diffuse bilateral infiltration, more extensive on the right. The patient received oxygen for five days. Because he was desperately sick, penicillin was given empirically (120,000 units daily) for six days without any significant effect. The condition improved gradually and the patient became afebrile in about five weeks. Roentgen resolution was very slow, as

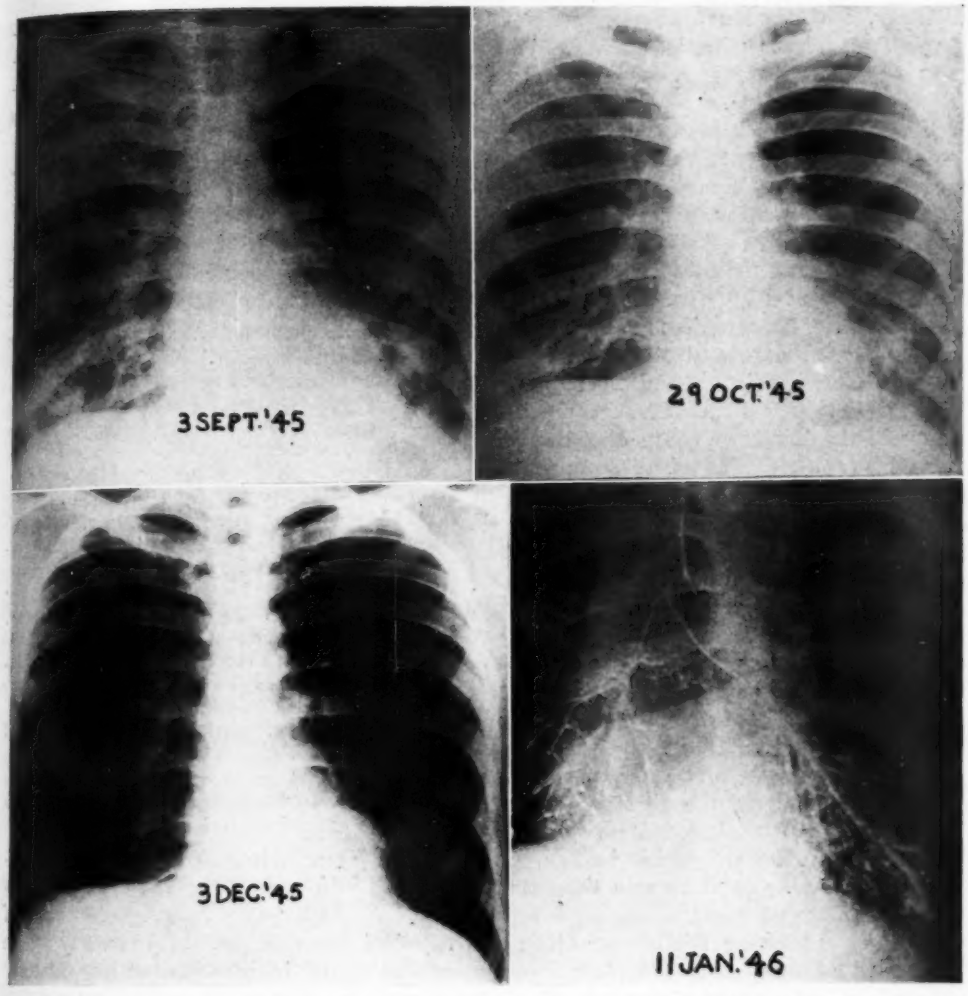

Fig. 6. Case 5: Successive roentgenograms (Sept. 3, Oct. 29, Dec. 3, 1945) of a patient with primary atypical pneumonia and subsequent development of bronchiectasis as shown by bronchography (Jan. 11, 1946).

observed on the film of Oct. 29 (Fig. 6) By Dec. 3, 1945 (Fig. 6), further clearing had occurred, with some residual basal linear infiltration, more evident on the left. Cough continued, with about 1 oz. of non-foul sputum daily. A liberal time interval was allowed to elapse before injection of lipiodol, to avoid a recurring pneumonitis. Finally, on Jan. 11, 1946, a bronchogram (Fig. 6) showed bronchiectasis in the posterolateral segment of the left lower lobe. Whether the affected lobe was permanently damaged cannot be stated, as this patient was transferred to a thoracic disease center nine days later.

DISCUSSION

The diagnosis of bronchiectasis and the prompt and proper disposition of the affected soldiers was the main medical obligation with respect to this disease at this hospital. For various reasons, bronchoscopy was not a routine procedure. Ideally, every patient with bronchiectasis should have at least one such examination. Unquestionably, significant intrinsic changes and an unsuspected foreign body may sometimes be discovered. Pending disposition, therapy consisted of symptomatic medication and postural drainage in those with moderate or excessive expectoration. A few patients received chemo-

therapy, sulfadiazine orally or penicillin parenterally, but the period of observation was too short to permit a definite conclusion as to its value.

The line of duty status was "yes" in 13 cases and the patients were transferred to general hospitals (thoracic disease centers) for further evaluation, according to army directives. For 88 patients the line of duty status was "no": 10 were returned to limited duty and 78 were separated from the service. These soldiers were instructed about their disease and strongly advised to have close medical attention on return to civil life. The curative effect of lobectomy in the hands of competent thoracic surgeons was emphasized to suitable patients.

In all fairness it should be mentioned that a number of patients were seen with a history of bronchopulmonary symptoms, frequently in association with abnormal physical and roentgen findings, in whom a presumptive diagnosis of bronchiectasis seemed justifiable but actual dilatation of bronchi could not be demonstrated by bronchography. These cases probably represent instances of bronchitis with or without some degree of pulmonary fibrosis. It is inevitable that there will be a percentage of normal bronchograms in any such clinical survey. At the same time there were encountered cases of doubtful bronchiectasis exhibiting slight variations of the so-called normal bronchial tree. As in other medical observations, the line of cleavage between normal and abnormal is sometimes imperceptible and subsequent re-examinations alone can make the final decision. In this connection, reference should be made to what Blades and Dugan (1) have described as "pseudo-bronchiectasis"—slight temporary bronchial dilatation which may follow primary atypical pneumonia and last for one to three months, with eventual reversion to normal. Such a term, however, is confusing; "reversible bronchiectasis," as used by Fleischner (2) is more logical.

Pneumonia, especially of the bacterial, lobular, and slowly resolving type, has long been recognized as an important etiologic agent in bronchiectasis. More recently, particularly during the war, primary atypical or "virus" pneumonia has attracted increasing attention, and the question of bronchiectasis as a complication in such cases deserves consideration. In what is probably the best article to date on the pathologic anatomy of atypical pneumonia, Golden (3) analyzed the changes in 42 autopsied cases. To quote:

> "The acute dilatation of affected bronchioles is observed fairly constantly. One would expect that complications might ensue, such as chronic bronchiectasis. To date no case in which this occurred has come to my attention pathologically. On the other hand, actual necrosis of bronchial walls was seen but once. In the remainder of the cases the lesions were of two types. In lesions of one type the bronchial walls were merely edematous, congested and heavily infiltrated with round cells. It is perfectly consistent with the known processes of repair that such lesions could resolve without leaving any appreciable damage. In lesions of the other type, frequently seen in the same case, one could demonstrate in small bronchi and bronchioles marked dilatation, destruction of the elastic fibers, fragmentation of the muscle bundles and shredding of the reticular meshwork. Such lesions probably could heal only by persistent dilatation and scar formation. This is not meant to imply that all such lesions could or would ever become clinically manifest as chronic bronchiectasis."

Kay (4) reported 20 cases of bronchiectasis (3 with reversible and 17 with permanent damage) following attacks of atypical pneumonia. Apparently none of his series had pulmonary symptoms prior to the pneumonia. The incidence of bronchiectasis was not known.

It may appear superfluous to mention that in this connection one should be certain that the patient was first afflicted with atypical pneumonia. There is no doubt that in the past few years this disease has been over-diagnosed in many army installations. The difficulty of differentiating borderline cases of atypical pneumonia from bacterial pneumonia and influenza is only too often apparent and the problem is further aggravated by the fact that secondary bacterial invasion may probably, in some instances, be superimposed on the virus infection. It should also be recalled

that acute inflammatory exacerbations may occur in association with pre-existing bronchiectasis and chronic interstitial pneumonitis.

At this hospital, bronchograms were done on patients with atypical pneumonia who had very slowly resolving or recurrent episodes with persistence of abnormal physical and/or roentgen signs. In only 9 cases was there definite evidence of bronchiectasis. Unfortunately this cannot be expressed on a statistical basis. Some of the remainder may represent, as Kay has suggested, intermediate changes in the development of bronchiectasis, but only a prolonged follow-up could furnish the correct answer. The problem is of interest and importance, and further study in this direction is necessary. One thing is certain: To minimize bronchiectasis as a complication, the ideal solution is to refrain from returning soldiers to duty until maximum clearing has occurred on physical and x-ray examination.

SUMMARY AND CONCLUSIONS

1. One hundred and one patients with bronchiectasis, diagnosed by bronchography, were admitted during a four-year period (1942–1945, inclusive) to a large army hospital. The pertinent clinical and roentgen features are reviewed.

2. The chief function at this hospital with respect to this condition was the diagnosis and proper disposition of the bronchiectatic patient. Eighty-eight soldiers had the disease prior to induction; 78 were discharged from the service and 10 were returned to limited military duty. Thirteen soldiers who contracted the disease in line of duty were transferred, according to army directives, to appropriate general hospitals for further study.

3. Bronchiectasis is a common disease. A plea is made for its early recognition. It may exist in the absence of classical symptoms and signs. The screening process on induction is not always conclusive. Furthermore, 39 of the hospitalized soldiers had negative or relatively negative plain roentgenograms. A careful history and a healthy suspicion of bronchiectasis will frequently lead to the diagnosis, but—

4. Bronchography is the only certain method of confirming the diagnosis. Several useful points in bronchography are mentioned. The anatomical distribution and the type of bronchial ectasia encountered in this series are tabulated. The left lower lobe was most commonly involved and cylindrical dilatation was most often noted.

5. The role of primary atypical pneumonia in the development of bronchiectasis is discussed.

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SUMARIO

Bronquiectasia en el Personal Militar

Durante un cuadrienio (1942–1945) ingresaron en uno de los más grandes hospitales militares de los E. U. A. 101 enfermos con bronquiectasia diagnosticada por la broncografía. Ochenta y ocho padecían de la enfermedad desde antes de su ingreso en el ejército: 78 fueron dados de baja del servicio militar y 10 fueron reintegrados en las filas. Trece que contrajeron la afección mientras servían en el ejército fueron trasladados para estudio ulterior a hospitales generales apropiados.

La bronquiectasia es una enfermedad frecuente, y aquí se aboga en pro de su reconocimiento temprano. Puede existir aun faltando los síntomas y signos clásicos.

Además, 39 de los soldados hospitalizados mostraron radiografías simples negativas o relativamente negativas. Un interrogatorio cuidadoso y una sospecha justificada de la existencia de bronquiectasia conducirán frecuentemente al diagnóstico acertado, pero la broncografía constituye el único método seguro para confirmarlo. La naturaleza e intensidad de la ectasia y su localización pulmonar pueden averiguarse fácilmente en esa forma. En la serie actual el lóbulo inferior del pulmón izquierdo representó el asiento más frecuente y la dilatación cilíndrica la forma predominante.

Discútese el papel desempeñado por la neumonía primaria atípica en la producción de la bronquiectasia pero sin llegar a conclusiones estadísticas.

Uptake of Radioactive Iodine by the Normal and Disordered Thyroid Gland in Children

A Preliminary Report

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STUDIES OF THE uptake of radioactive iodine by the normal and hyperfunctioning thyroid gland in adults have been published by Hamilton and Soley, Hertz, Roberts and Salter, (1, 2) and others. Hamilton, Soley, Reilly, and Eichorn have reported on iodine studies in a small series of cases of childhood hypothyroidism, including some with goiter (3). Most of their tests were made with eight-day iodine containing an appreciable admixture of stable iodine; with such material the apparent uptake is always much less than with a "carrier-free" preparation in which all the iodine is radioactive.

Since the search for an unambiguous indicator of thyroid function in children, particularly in infants, still continues, the present study was undertaken in the hope of achieving this goal..

Eight-day radioactive iodine (I^{131}), carrier-free, was obtained from the cyclotron laboratory of the Massachusetts Institute of Technology in dilute solution of sodium iodide. The amount of the latter was so small as to be considered physiologically negligible. The material was administered quantitatively by mouth, a stomach tube being used in the case of infants and uncooperative small children. The subjects were not fasted. The doses varied from 20 to 40 microcuries (containing not more than 2 micrograms of iodine) in about 20 c.c. of solution. Smaller amounts were given to babies than to older children, but they were not calculated accurately on a weight basis.

The relative quantities of the iodine concentrated in the thyroid glands were determined by measurements with a shielded Geiger counter placed in a fixed position over the front of the neck. These were related to the administered doses by measurements in the laboratory with a "phantom" set-up approximating the geometrical relationships with the patient. Whenever possible, all urine was collected for two successive 24-hour periods for measurement of the amount of iodine excreted.

Pathological cases were selected chiefly on the basis of medical interest; this resulted in the study of infants and children of from three weeks to fourteen years. To eliminate differences in uptake due to possible variations in the material received from the cyclotron, an effort was made to study a control child of the same age and of approximately the same size simultaneously with each patient. The controls all came from the hospital population. While none showed features which justified the suspicion of "glandular" disorder, no matter how vague, only a few were strictly well children. The majority were suffering from, or in convalescence after, various illnesses, such as infection, diarrhea, or nutritional disorder, which can certainly be conceived to have affected temporarily the state of activity of the thyroid gland. The precaution of studying a control at the same time as the patient proved unnecessary, since significant variations in the quality of the test material were not detected.

Fifty-four subjects are included in this report; two or three tests were done on a few. Twelve were infants under one year. Of these, 11 were controls; the other had

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TABLE I. PER CENT OF RADIOACTIVE IODINE IN THYROID GLAND IN CONTROLS AT 48 HOURS AFTER ORAL ADMINISTRATION

Infants to 1 year		Children 1–4 years		Children 5–14 years	
Name	Per Cent	Name	Per Cent	Name	Per Cent
T. P.	10	E. G.	10	M. B. (adult)	10
M. F.	7	P. M.	4	L. A.	15
P. C.	15	D. A.	7	B. B.	9
J. L.	15	R. H.	11	L. R.	18
W. T.	10	J. G.	12	A. P.	15
J. B.	11	G. M.	15	H. G.	13
V. P.	9	E. S.	10	R. E.	12
H. V.	12		—	J. P.	20
P. T.	9	Average	9.9	M. M.	15
M. F.	20	σ =	3.3	S. T.	13
E. G.	17			M. C.	11
				A. R.	12
Average	12.3			R. P.	17
σ =	3.7			E. S.	12
				D. D.	12
				Average	13.5
				σ =	2.9

Total mean 12.0 σ = 3.6

been recognized as a cretin at the age of three weeks. Fifteen were between one and four years of age; 7 were controls as defined above; 2 were classical cretins; 1 showed some features of hypothyroidism which were not modified by treatment; 2 were dwarfs; in 1 the diagnosis was "gargoylism"; 1 was suspected of progeria, a disorder associated with some of the features of hypothyroidism, and the last exhibited features of moderate sexual precocity. Twenty-seven were more than four but less than fifteen years of age. Of these 2 had unmistakable hypothyroidism, 2 Graves' disease, 1 questionable hyperthyroidism. Four were dwarfs; of these, 1 showed debatable signs of reduced thyroid function. One had a colloid goiter of small dimensions and showed no evidence of alteration of thyroid function. One had an adrenal pheochromocytoma, and 1 idiopathic hypoparathyroidism without evidence of hypothyroidism. Fifteen served as controls—again in the sense already defined.

Measurements on a few children were started shortly after administration of the material and carried out at intervals through the day for several days thereafter. Others were measured only daily for a few days and then at longer intervals. It was found that the values are substantially constant from the first through the fourth day, when correction is made for radioactive decay. Therefore, for convenience of comparison, the 48-hour reading was arbitrarily selected. These 48-hour readings for the controls are given in Table I, with averages and standard deviations.

Measurements of excretion were possible in only the five- to fourteen-year group and not in all of these. Some specimens were frequently lost. The available data for controls are given in Table II. It appears that excretion is rapid and that the totals are fairly constant but would not be satisfactory as an index of uptake.

Table III presents the data relating to the concentration of iodine in the neck region of the hypothyroid and hyperthyroid individuals and of those who had, or for one reason or another may be considered suspect of, some endocrine disorder.

The few observations that were made on the excretion of iodine in the urine of these individuals appear in Table IV.

DISCUSSION

In view of the preliminary character of this communication and the limited nature of the data, it does not appear warranted to discuss them in great detail.

As regards the controls, the mean value for uptake is 12.0 per cent with a standard deviation of 3.6.

One feature stands out in the group of abnormal subjects, namely, the extremely small retention in the case of the individuals with indisputable hypothyroidism. J. A. suffered from complete athyreosis occasioned by the inadvertent removal of a small, spherical mid-line undescended thyroid gland which was erroneously taken to be a thyroglossal duct cyst. Her uptake was essentially zero. The cretins, although their defect of glandular substance appeared to be complete on clinical grounds, concentrated enough iodine to suggest that traces of the gland were present, thus confirming a common anatomic observation in cretinism.

TABLE II: URINARY EXCRETION OF RADIOACTIVE IODINE IN CONTROLS
(Per Cent of Oral Dose)

Case	0–8 Hours	8–16 Hours	16–24 Hours	24–48 Hours	Total
L. R.	44	28	4	3	79
A. P.	33	19	13	4	69
R. E.	25	25	8	9	77
M. C.	7	21	10	7	Incomplete
R. P.	13	35	5	13	66
D. D.	25	9	No specimen	12	Probably incomplete
E. S.	Two days' specimens assembled				68
A. R.	44	8	Incomplete	0	Incomplete
J. P.	49	0	11	2	62
C. P.	Lost	25	11	19	Incomplete

TABLE III: PER CENT OF RADIOACTIVE IODINE IN THYROID GLANDS OF ABNORMAL SUBJECTS

Case	Diagnosis	Age	Per Cent Uptake, 48 hr.	Per Cent Excretion, 48 hr.
Known Thyroid Disorder				
S. B.	Sporadic cretinism	2 mo.	Less than 1	
E. M.	Sporadic cretinism	16 mo.	Less than 1	
T. A.	Sporadic cretinism	2 yr.	Less than 1	
L. B.	Sporadic cretinism	14 yr.	Less than 1	
J. A.	Surgical myxedema	12 yr.	Less than 1	70
J. R.	Graves' disease	9 yr.	60	Less than 10
J. M.	Graves' disease	10 yr.	34	
V. S.*	Slightly enlarged thyroid Probably diffuse colloid goiter	14 yr.	20	49
C. P.	Colloid adenoma of thyroid No evidence of hypothyroidism	12 yr.	3	
	Repeated test		3	71
Other Abnormals				
A. P.	Dwarfism	7 mo.	6	
L. G.	Dwarfism; extremely questionable hypothyroidism, non-responsive to treatment	2 yr.	8	
J. F.	Dwarfism	2 yr.	6	
D. K.	Dwarfism; questionable hypothyroidism	7 yr.	5	
A. N.	Dwarfism	8 yr.	21	54
M. N.	Dwarfism; nutritional difficulty	9 yr.	17	44
P. F.	Dwarfism	12 yr.	0.5	87
D. O.	Progeria (?) After 2 months on thiouracil Four months after stopping thiouracil	16 mo.	30 11 21	
D. T.	Gargoylism	2 yr.	9	
L. B.	Slight sexual precocity Adrenal-cortical tumor (?)	3 yr.	21	
S. H.	Hypoparathyroidism (idiopathic) No evidence of hypothyroidism	10 yr.	6	
D. B.	Pheochromocytoma of adrenal	12 yr.	13	64

* This patient had been on iodine therapy for six months; it had not been discontinued prior to the test. Her basal metabolic rate, cholesterol, and blood iodine were all normal. She was suspected of hyperthyroidism but could not be expected to show an elevated radio-iodine uptake under these circumstances.

With the exception of the patient mentioned in the previous paragraph, only patients with clear-cut hypothyroidism had values so low. However, *quite* low concentrations were observed not only in those individuals who presented unequivocal evidence of hypothyroidism but also in some who failed entirely to suggest this possibility. Attention may be drawn to P. F., a white boy of twelve years whose stature was about that of a six-year-old. The history, physical features, and laboratory evidence pointed to non-endocrine dwarfism or, at most, to dwarfism due to unique deficiency of the growth-promoting secretion of the hypophysis. The low re-

TABLE IV: EXCRETION OF RADIOACTIVE IODINE IN THE URINE OF ABNORMAL SUBJECTS
(Per Cent of Dose)

Name	0–8 Hours	8–16 Hours	16–24 Hours	2d Day	3d Day	Total
J. A.	First 24 hours.....		.32	32	6	70
Y. S.	First 24 hours.....		.30	19	..	49
J. R.	8	Less than 1	Less than 1	Less than 1	..	Less than 10
P. F.	50	3	20	14	..	87
A. N.	30	4	14	6	..	54
C. P.	Lost	25	11	12	..	Incomplete
Repeat	35	15	16	5	..	71
D. B.	9	16	11	8	..	64
M. N.	..	..	39	5	..	44

tention and rapid excretion of iodine can certainly not be ascribed to hypothyroidism of any recognizable variety or degree. Since the boy came from a part of the country where iodized table salt is commonly used, saturation of the gland is a possible explanation, but the history failed to reveal information on this point. His basal metabolic rate, calculated by three standards, was +60. However, this is doubtless wrong. It should be pointed out that there are no satisfactory standards for dwarfs. C. P. had a small colloid adenoma of her gland but was normal in all other respects. The idiopathic or cryptogenic hypoparathyroidism which S. H. exhibited was not accompanied by any signs whatever of reduced function of the thyroid gland.

A second but somewhat less impressive feature in the group of abnormal subjects is the high value in the two cases of Graves' disease and the elevated retention in the single case of what is probably progeria.

As was stated in the introduction, the excretion of iodine in the urine was confirmatory of the uptake by the gland. Discrepant results should serve to call attention to the possibility of technical error in one or the other of the measurements or to the loss of specimens of urine. Since in young children the need to collect urine quantitatively over a considerable period of time imposes a serious restriction on the feasibility of any test, this part of the study has not been pursued with great zeal.

CONCLUSIONS

The administration to infants and children, by the oral route, of carrier-free radioactive iodine in doses of from 20 to 40 microcuries is followed by concentration and retention within the thyroid gland of amounts which vary from about 12 per cent in those without evident thyroid disorder, upward to severalfold this value in hyperthyroidism and downward to less than 1 per cent in those who are typically hypothyroid. Values considerably below the mean, and occasionally as low as those in unmistakable hypothyroidism, are found not only in individuals who are only dubiously hypothyroid but also in some whose thyroid function is quite beyond clinical suspicion of insufficiency. These limitations to interpretation doubtless depend in part on the fact that hyperthyroidism and hypothyroidism are both relative states and show variability of degree. However, non-numerical examination of the data suggests that sharper results could be obtained by more careful standardization of the test with respect, among other things, to the patient's previous intake of iodine and the state of his health at the time of the observation.

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SUMARIO

Absorción de Yodo Radioactivo por el Tiroides de los Niños

La administración a los niños, incluso lactantes, de yodo radioactivo, sin portador, por vía bucal, a dosis de 20 a 40 milicuries va seguida de concentración y retención en el tiroides de cantidades que varían de aproximadamente 12 por ciento en personas sin distiroidia manifiesta a varias veces dicha cifra en el hipertiroidismo y menos de 1 por ciento en los hipotiroideos típicos. Encuéntranse cifras considerablemente inferiores al promedio, y de cuando en cuando tan bajas como las del hipotiroidismo indudable, no sólo en individuos dudosamente hipotiroideos sino también en algunos cuya función tiroidea queda más allá de toda sospecha clinica de insuficiencia. Estas limitaciones de la interpretación dependen sin duda en parte de que tanto el hipertiroidismo como el hipotiroidismo son estados relativos de intensidad variable. Sin embargo, el estudio no numérico de los datos disponibles indica que cabría obtener resultados más netos mediante una estandardización más cuidadosa de la prueba con respecto, entre otras cosas, a la previa ingestión de yodo por el enfermo y el estado de su salud en la fecha de la observación.

(*For discussion of this paper, see page 229*)

Preparation of Radioautographs of Thyroid Tumors for Study at High Magnification[1]

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ONE OF THE methods of studying iodine uptake of thyroid tumors is to make radioautographs of thin sections of the tissue. The usual procedure (1–4) is to place the tissue section, mounted on a microscope slide, against a photographic emulsion for a suitable time in the dark. After the radiation exposure, the two plates are separated. The photographic image is developed, the tissue section is prepared for histologic examination, and the two are compared. In most instances the autographs give clear evidence as to whether the tissue has accumulated radioiodine and, if so, in what general region. The plate containing the autograph may be superimposed on the tissue preparation to permit further localization of the radioiodine. With this method, the exact location of the radioiodine is difficult to determine, as at higher magnifications the alignment of the two preparations becomes arbitrary and the outlines of the denser areas of the autograph are not distinct.

It is apparent that closer contact between the tissue and the photographic plate is to be desired; also, that a more objective alignment of the tissue and autograph would be obtained if the two did not have to be separated after the radiation exposure had been made. It occurred to us that, as one of the standard procedures in microtechnic is to float paraffin sections onto the microscope slide, it would be worth while to try such a method of mounting tissue directly on a photographic plate. It seemed probable that the tissue would adhere to the photographic emulsion and would permit passage of the photographic chemicals as well as those used in the histologic technic. At the time that preparations for this experiment were under way, a method of attacking this problem was published by Bélanger and Leblond (5). This consists of removing the emulsion from an unexposed lantern slide and spreading it over the tissue section. After proper exposure to the radioactive material contained in the tissue, the emulsion is developed and fixed. The preparation is then subjected to the usual histologic staining procedures. This method permits close contact between the tissue and the photographic plate. Also, the histologic preparation and the autograph are automatically superimposed.

This method seemed to offer a solution of the problems outlined above, so it was tried along with the usual technic. The results were better than with the older method, but several objectionable features developed. The transposed emulsion varied in thickness, developed a heavy "fog," softened easily, and tended to lift away from the tissue section. The emulsion became heavily stained, and study at high magnification was difficult. No doubt some of the faults were due to inexperience and could have been eliminated in time. It seemed advisable, however, to try mounting the tissue directly on a photographic plate. This method has been found to be satisfactory, and results are much better than those previously obtained.

Sections of thyroid adenoma, etc., containing radioiodine produce good tissue autographs as the follicles are usually surrounded by stroma so that the localization is more distinct than when several follicles are close together and their radiation fields overlap. This report will be limited to a demonstration of results attainable with radioiodine in human thyroid tumors, but the method is applicable to other radioactive substances and other tissues as well. The thyroid region of the rat was employed

[1] Accepted for publication in March 1947.

during the preliminary studies in which the method was developed (6).

MATERIAL AND METHODS

After the thyroid tissue containing the radioiodine has been preserved, dehydrated, and embedded according to usual histologic procedures, the paraffin sections are cut at 10 μ or less. The ribbon is separated into groups containing two or more sections. These are then placed on the surface of water in a Petri dish at the proper temperature to produce spreading of the sections (approx. 42° C.). After the sections have expanded, the Petri dish is taken into the photographic darkroom and dropped gently into a larger bowl of cool water, allowing the ribbons to float free. Then, in the dark and in front of a dim red safe-light, the red insensitive film or plate is slipped under a strip of tissue sections. The strip is held against the emulsion with a needle or small brush, and the plate plus the tissue is removed from the water. The preparation is dried and stored upright in a light-tight box. The following day the plates are immersed in xylol until the paraffin has been removed. The plates are then returned to the storage container until the radiation exposure has been completed. The proper exposure time is determined by trial and by amount of activity as indicated by the Geiger counter. When the exposure to the radiation has been completed, the photographic plate with the tissue section still in place is developed, fixed, and washed, and is allowed to dry before further processing. The tissue is then stained with Harris' hematoxylin (over stain-wash-acid water-wash-alkaline water-wash) and counterstained with eosin. The preparation is dehydrated in alcohols, cleared in xylol, and mounted in clarite, or balsam.

Lantern slide plates, Eastman median contrast, are satisfactory for the autographs. The 2 × 2-inch size is convenient for the tissue-autograph preparation and the 3 1/4 × 4 1/4-inch size is used for the older method in which the microscope slide containing the tissue is taped to the photographic plate during the radiation exposure. It is best to produce both types of autographs as a check on proper development and penetration of solutions, etc. The lantern slide plates are reasonably radiosensitive, the grain is fairly uniform, and it is possible to stain the tissue section on the plate without making the color of the emulsion too heavy. The tissue-photographic plate preparation should be dried as often as possible, solutions should not be warm, and strong acids are to be avoided.

Dental x-ray film (Eastman ultra-speed safety film) is more sensitive to the radiation, but the final preparation is not as clear as when lantern slides are used. The film is used when quick results are desired. Recently, sections of a thyroid adenoma containing radioiodine produced satisfactory autographs with a radiation exposure of only sixteen hours. An hour later the preparations had been stained, mounted in glycerine jelly, and were being studied under the microscope. Permanent preparations may be made with film, but the staining of the film is heavy and it tends to curl in the xylol. Coloring of the film may be avoided to some extent by staining the tissue *in toto* (acetocarmine or alcoholic eosin) as it is being preserved. Care must be exercised, however, not to wash out the stain completely in subsequent treatment, and a counter stain must be added after the tissue has been mounted on the film. If the film is dried in air, after the tissue has been stained, then rapidly put through the alcohols and xylol, the tendency to curl will not be great. The film may then be trimmed, mounted in balsam, and held flat while drying by means of a small weight on the cover slip. The tissue may also be stained with Harris' hematoxylin (either before dehydrating, or later as the sections are spreading in the warm water) before it is placed on the film, but again most of the stain is lost in subsequent treatment. A mordant, ferric alum, may be added to the preservative (7) so that later, when the tissue-autograph preparation is immersed in iron hematoxylin, the

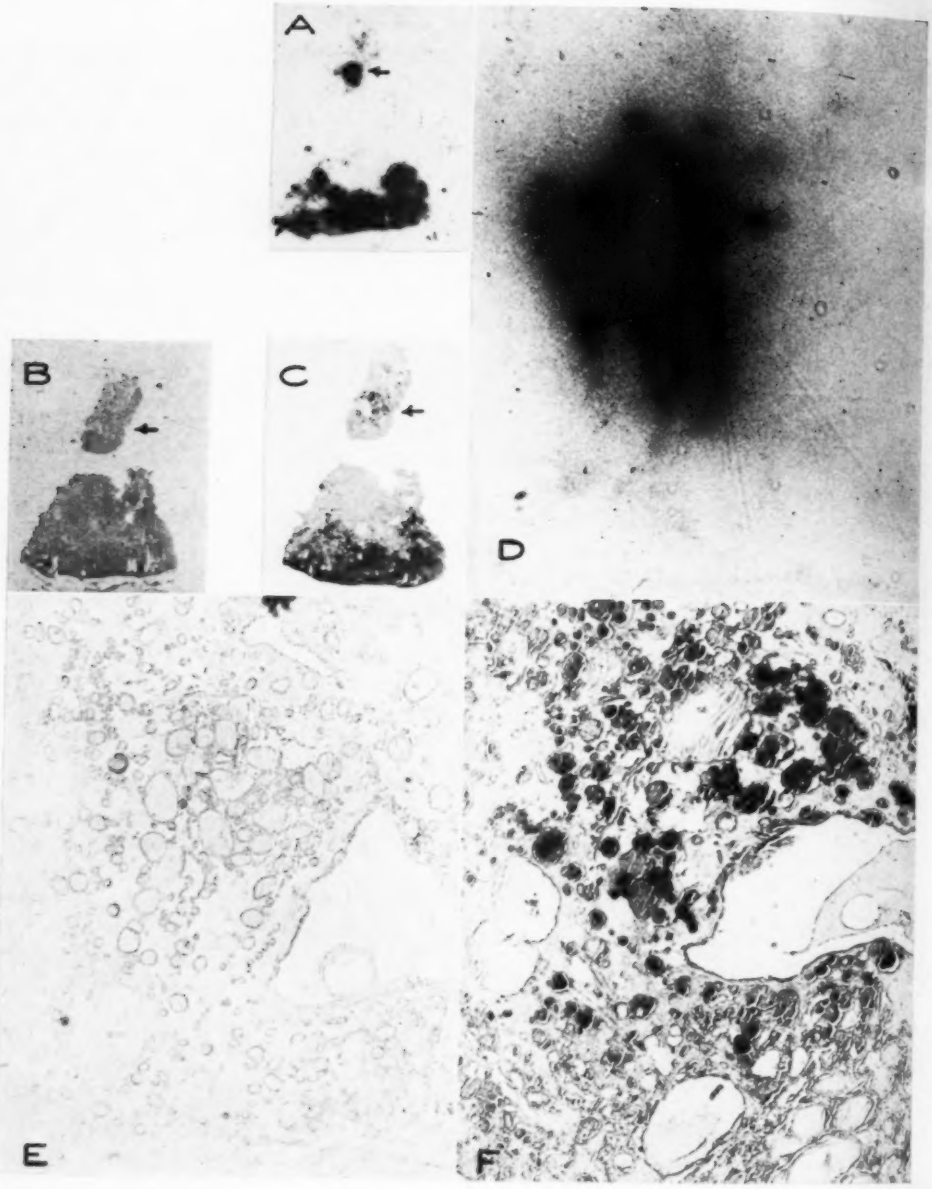

Plate I. A. Radioautograph (× *c.* 2.15) of a section of thyroid adenoma containing radioiodine. Made by placing tissue section (mounted on microscope slide) against a photographic plate.

B. Photomicrograph of the tissue section used in making the above radioautograph (× *c.* 2.15). The section has been inverted so as to give orientation similar to that of *A*.

C. Photomicrograph (× *c.* 2.15) of tissue-autograph preparation, inverted to correspond in position with *A* and *B*, of a section from the same block of tissue used for *A*.

D. Photomicrograph of a portion of the autograph image, marked with arrow in *A*, at higher magnification (× *c.* 33).

E. Region of *B*, marked with arrow, × *c.* 33. The relative positions of left and right sides have been reversed as compared to above figures.

F. Tissue-autograph preparation oriented similarly to *E* and at the same magnification. One should not attempt to identify details of Fig. *F* in Fig. *E*, as they are many sections apart, although from the same general region. The follicles containing the radioiodine are indicated by darkened areas of the photographic emulsion, which is in place directly under the tissue.

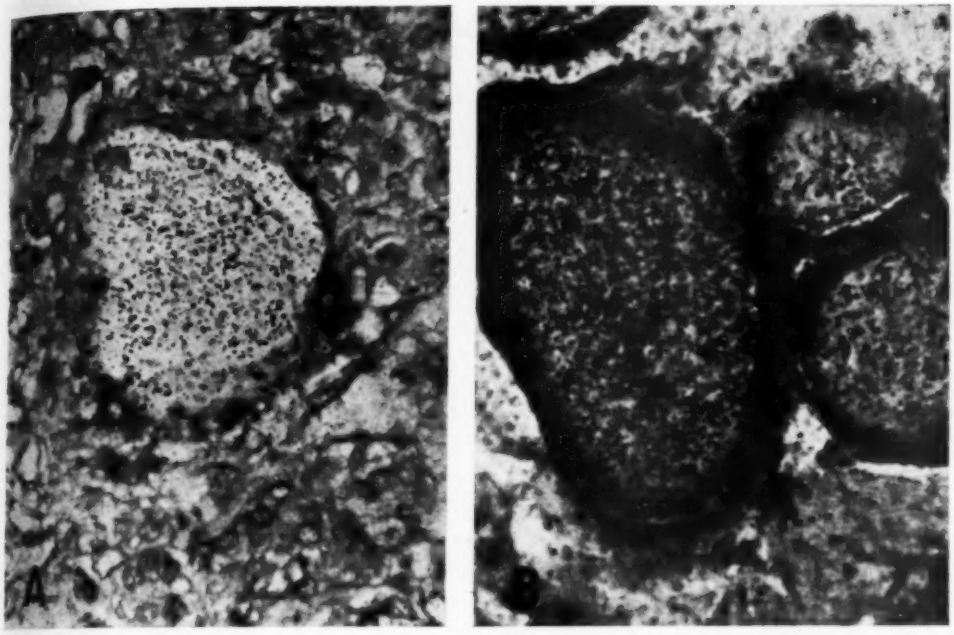

Plate II. A. Photomicrograph (× *c.* 520) of thyroid adenoma section mounted on photographic plate. The individual grains of reduced silver in the emulsion may be seen. Enough of the photographic image was in the same plane of focus as the tissue to permit this single picture showing the heaviest concentration of radioiodine to be within the follicle.

B. Photomicrograph (× *c.* 620) of section of another thyroid adenoma mounted directly on photographic emulsion. The plane of focus is slightly below that of the cells, and the heavy accumulation of reduced silver grains may be seen in the region of the colloid.

tissue is selectively stained. Caution must be used if ferric alum is employed to differentiate after hematoxylin, as it acts to reduce the photographic image to some extent.

If it is desired to reduce the photographic image, the plate may be immersed in iron alum or a weak solution of permanganate (8) until the desired contrast has been reached.

RESULTS

Two surgical specimens of thyroid adenoma were provided through the courtesy of Dr. V. Kneeland Frantz, Department of Surgical Pathology. These patients had been given 1 mc. of I^{131} twenty-four hours before removal of the glands. Material was removed from these adenomas, and regions indicating the presence of radioiodine (detected by Geiger counter) were preserved in Bouin's solution, dehydrated, and embedded in paraffin. Sections were cut at 10 μ. An autograph made in the usual way, *i.e.*, slide bearing tissue separate from photographic plate, is shown in Fig. *A* of Plate I. The corresponding tissue section is shown in Fig. *B* of this plate. It is easy to determine the general location of the radioiodine with an autograph as distinctive in pattern as this one. It may be determined by inspection and by measurement that the radioiodine is chiefly at the base of the triangular section and in the lower part of the upper section. Further localization is difficult, as at high power a certain region of the autograph appears very diffuse (Fig. *D*, Plate I). It is not easy to match Fig. *D* with Fig. *E* to determine the exact location of the radioiodine. The tissue-autograph preparation at low magnification (× 2.15) is shown in Fig. *C* of Plate I. Although this specimen is many sections removed from that of Fig. *B*, it is from the same region of the tumor,

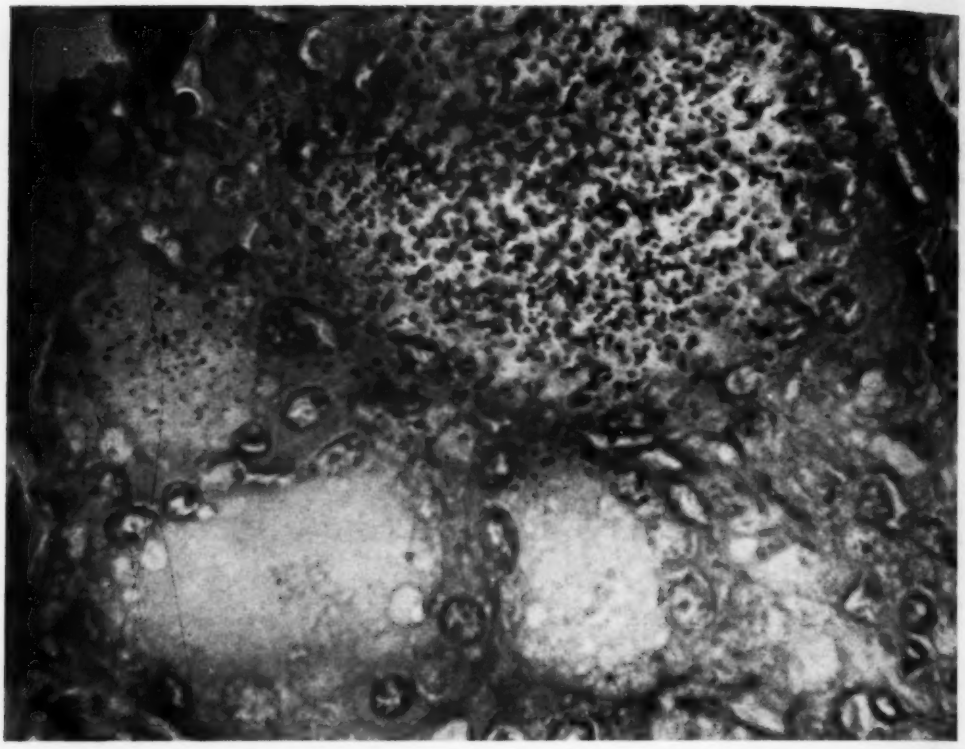

Plate III. Photomicrograph of tissue-autograph preparation at high magnification (× *c.* 950). The plane of focus is just below that of the tissue. Sections were cut at 5 μ and mounted on a 2 × 2-inch medium contrast lantern slide. The exposure time was seven days. An estimate of the amount of contained radioactivity was obtained by placing a section 2 cm. below an unshielded (Technical Associates) beta-ray-counting Geiger tube. The activity, with this arrangement, was 91 counts per minute.

and the regions of accumulated radioiodine appear to be the same as shown in the autograph (Fig. *A*). As the tissue remains in place on the photographic emulsion, proper alignment is automatic and the tissue-autograph preparation may be examined at higher magnification, as in Fig. *F*, Plate I. The region shown in this figure is that marked with an arrow in Fig. *C*. In order to photograph this region at high magnification, the preparation was turned over so that the thin cover-slip would allow the objective to come close enough to focus on the tissue. Sections shown in *B* and *C* were photographed through the microscope slide side in order that the orientation would be the same as in *A*. Therefore, the left sides of Figs. *F*, and *E*, are opposite to those of the other figures in this plate. The follicles shown in Fig. *F* are not the same as those of Fig. *E*, but the section is through the same general region. The photomicrograph (× 33) of the tissue-autograph preparation (Fig. *F*) shows that the radioiodine is apparently concentrated in the small follicles and in some of the larger ones. The preparation was made on a lantern slide and stained with Harris' hematoxylin and eosin.

The tissue-autograph preparations may be studied at higher magnification, and as one changes from the low-power objective to the higher power, the plane of the tissue and that of the autograph become more distinctly separate. Both images may be visualized simultaneously by focusing up and down rapidly with the fine adjustment of the microscope. Fig. *A* of Plate II is a

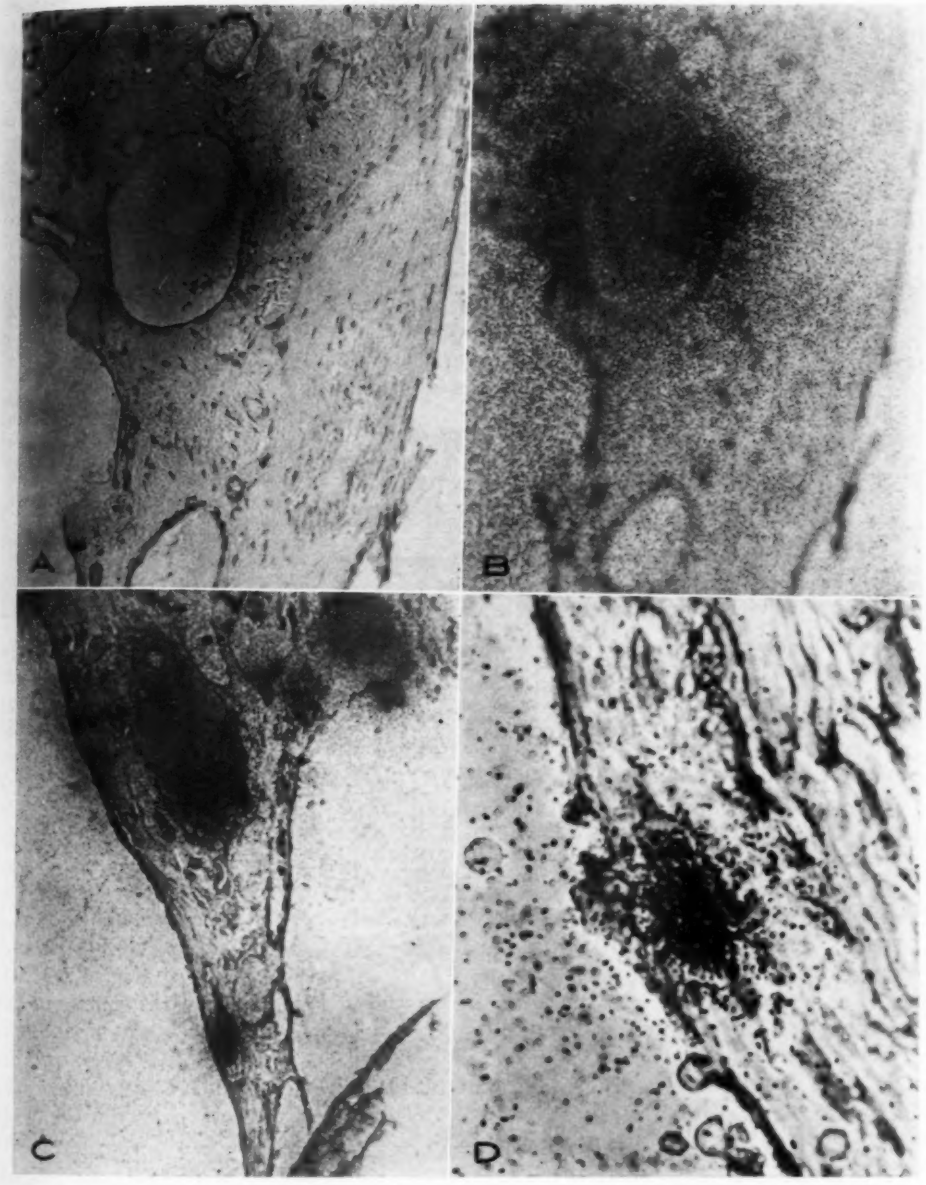

Plate IV. A. Photomicrograph of a section of thyroid carcinoma superimposed on the autograph, which had been exposed and developed separately. The plane of focus is that of the tissue (× *c.* 100).

B. Photomicrograph (× *c.* 100) of same tissue section and autograph as in *A*, with the autograph in focus. It may be seen that localization of the reduced silver grains is not good, even though the autograph and tissue appeared to match at lower magnification.

C. Photomicrograph (× *c.* 100) of preparation in which tissue is mounted directly on photographic emulsion. The plane of focus is intermediate between that of the tissue and of the autograph. It may be seen that localization, indicating presence of radioiodine, is much better than that shown in *A* and *B*.

D. Photomicrograph (× 640) of a small region of same tissue as above figures. In this tissue-autograph preparation at high magnification the individual grains of reduced silver may be distinguished. An approximation of the resolution attainable with this method may be obtained by using the diameter of erythrocytes present as a scale.

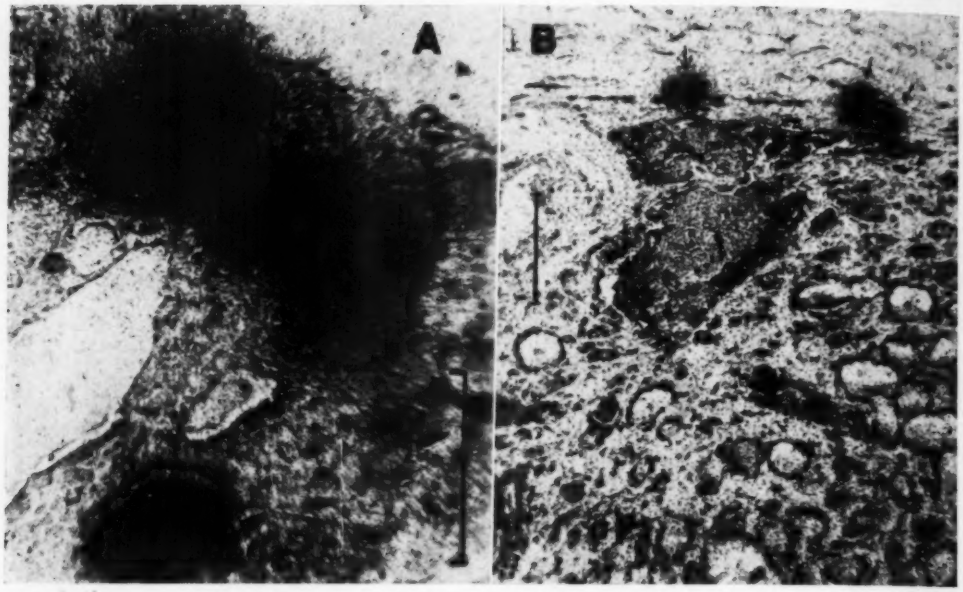

Plate V. A. Photomicrograph of tissue-autograph preparation (× 300, scale 100 μ) from tissue taken from a thyroid carcinoma. The plane of focus is intermediate between that of the tissue and that of the autograph. Areas of heavy radioiodine concentration are indicated by the darker regions.
B. Photomicrograph of tissue-autograph preparation (× 160, scale 100 μ) from thyroid-carcinoma metastasis. Regions of accumulated radioiodine are indicated by the arrows.

photomicrograph of a follicle and adjacent tissue from the second case of thyroid adenoma. At this magnification (× *c.* 520), it is not possible to photograph all of the developed grain in the same plane with the tissue. The photograph actually shows a better localization of the grain within the follicle than does the preparation viewed through the microscope. In the microscope field, by focusing up and down, one sees that, although there is a greater concentration of dots under the follicle, there is considerable "background" underneath all of the tissue. Three follicles of the first case are shown in Fig. *B* of Plate II at a magnification of *c.* 620. The focus here is just below that of the tissue. The grain appears dense within the follicles and extends with decreasing density beyond their boundary. Plate III shows a small region of an adenoma highly magnified (× *c.* 950). The amount of reduced silver is high under the upper follicle, is slight in the smaller one to the left, and there is practically none in the two lower ones.

Tissue-autograph preparations have been made of two autopsy specimens of thyroid carcinoma sent to us by Dr. S. M. Seidlin, Miss Eleanor Oshry, and Dr. A. A. Yalow of Montefiore Hospital. Examples from the first case are shown in Plate IV. The "regular" autograph presents no distinct pattern, but by superimposing the histologic preparation on the autograph (so that previously made marks on the two coincide) it is possible to obtain satisfactory matching at low magnification. Under slightly higher magnification it is found that the autograph is diffuse, and critical alignment is difficult (see Figs. *A* and *B*, Plate IV). In the tissue-autograph preparation the alignment remains intact and localization of the radioiodine is evident (Figs. *C* and *D*, Plate IV).

The "regular" autographs (histologic preparation separate from autograph), not shown in this paper, of the second case of thyroid carcinoma are more distinctive in pattern and serve to check the findings of the tissue-autograph studies. A critical

analysis of these cases will be published by the investigators concerned. However, brief mention of some of these observations serves to call attention to the type of detailed information that may be gained by employing tissue-autograph preparations. For instance, it appears that in the adenomas there is some correlation between radioiodine uptake and appearance of the tissue (heavy in growing follicles, diffuse in larger ones, and lacking in degenerating ones). The concentration of radioiodine was less consistent with the appearance of the tissue in the carcinomas. It may be seen in Fig. *A* of Plate V that some of the follicles concentrated radioiodine and adjacent ones contain much less. In Fig. *B* of Plate V the concentration of this dose of radioiodine appears not in the region of follicles but in the stroma, where small groups of cells are apparently beginning to function. One should not consider this finding as general, as we have recently examined metastases from another case of thyroid carcinoma in which the more differentiated regions contained the heavier concentration of iodine.

It is evident from the illustrations and the above discussion that tissue autograph preparations will aid in the study of thyroid function and may help in determining whether a certain case of thyroid neoplasia should be treated with radioiodine.

SUMMARY AND CONCLUSIONS

By mounting the tissue section directly on the photographic emulsion, it is possible to obtain radioautographs which are automatically in alignment with the histologic preparation. This allows, in effect, a differential "staining" of either large or minute regions that have concentrated radioiodine within a certain period of time.

NOTE: It is a pleasure to acknowledge the technical help provided by Miss Grace Clarke, Miss Estelle Sobel, and the other assistants of the laboratory. The writer is also indebted to Dr. G. Failla and Dr. Edith Quimby for their advice and encouragement.

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SUMARIO

Radioautografías de los Tumores Tiroideos

Las preparaciones histo-autográficas ayudarán en el estudio de la función tiroidea y pueden ayudar a determinar sin debe o no tratarse con radio-yodo un caso dado de neoplasia tiroidea.

Montando el corte histológico sobre la emulsión fotográfica es posible obtener radioautografías que automáticamente alinean con la preparación histológica, lo cual permite, en efecto, la "coloración" diferencial de regiones ya extensas o minúsculas que han concentrado radio-yodo dentro de cierto período de tiempo.

Cancer of the Prostate[1]

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Director of the Institute of Radium, Santiago, Chile

IN VIEW OF THE recent work on the treatment of carcinoma of the prostate by estrogens on the one hand and by castration on the other, sometimes supplemented by irradiation of the suprarenals or the pituitary, the following report of 25 cases treated in the past ten years is presented. Fourteen of this number were proved by biopsy; in the remainder, diagnosis was based on clinical findings.

In a paper presented before the American Urological Association in 1944, Alyea (1) pointed out that, while the good immediate results of castration or diethylstilbestrol in prostatic carcinoma are now established, certain questions remain to be answered: How long will the palliative effects persist? Will the patient live longer and in greater comfort? Are metastases delayed or prevented? Which is to be preferred, stilbestrol or orchiectomy, or a combination of the two? Alyea's own series of cases, treated by orchiectomy, numbered 110 and included 40 in which the operation had been done between two and three years earlier. From his personal observations and a review of reported series, he concluded that life is prolonged and made more comfortable, though palliation is frequently temporary. His last two questions he was unable to answer, but his own preference, so far as treatment is concerned, was for orchiectomy plus small doses of stilbestrol postoperatively to inactivate extragonadal androgens.

Stirling (18), in a paper presented at the same meeting, concluded that, while castration and estrogen therapy seem to be palliative, they neither prevent recurrence nor retard metastasis. Neither procedure, he believed, would completely eliminate androgenic activity.

Munger (13), in a discussion of the foregoing papers, placed testicular irradiation on a par with surgical castration, attributing to each appreciable temporary improvement. He did not consider estrogen alone a sufficient adjunct to these measures. For maximal stabilization he advised regional irradiation to and including the level of the adrenals. Such irradiation, he felt, given coincidentally with the administration of estrogens, enhances the efficacy of their attack on the extragonadal hormonal depots.

Wattenberg and Rose (21) have distinguished between the secretory and growth functions of the prostatic cancer cells, holding that the growth factor is influenced during estrogen therapy by the change in secretory function. The acid phosphatase, which is the enzyme produced by the carcinoma, may fall to a low level following administration of estrogen, with consequent retardation of tumor growth, but sooner or later, even with a diminished secretory function, the growth function will gain momentum. Furthermore, some carcinomas have a low secretory function but an active growth function, and in such cases x-ray therapy will be required.

Huggins (10), five years after the introduction of endocrine therapy of prostatic cancer—in the form of orchiectomy or administration of estrogens—sought to evaluate the results of such treatment. In 18 or 20 cases treated by orchiectomy he obtained remissions of varying duration, though the disease was far advanced, with widespread skeletal metastases and an elevated serum phosphatase. Five patients were alive after five years, 4 with no evidence of tumor, but no claims of cure are made. Huggins concludes merely that "the antiandrogenic therapy of can-

[1] Accepted for publication in December 1946.

cer of the prostate demonstrates that a chemical change in the internal environment of the host has brought about a long-continuing regression of a malignant neoplastic process."

As suggested above, it is these and similar reports that have led me to a review of my own cases. First, however, it may be well to say something about the incidence of prostatic carcinoma. According to the statistics of the Metropolitan Life Insurance Co., carcinoma of the prostate accounted for 1.5 per cent of 127,740 cancers in their total number of insured. This figure is in close agreement with that of Randall (16), who found an incidence of 1.3 per cent in a series of 1,215 necropsies. Herzog (9), of Concepción, Chile, believes that 2.25 per cent of all cancers in men involve the prostate, and Moore (12), reviewing the prostatic findings in a consecutive series of autopsies, points out the rising incidence with advancing age. For 229 men dying between the ages of 51 to 90 the figure was 21 per cent.

The high incidence of prostatic carcinoma in older men is explained by the frequent occurrence of malignant change in the hypertrophied prostate. Ewing believed that 33 per cent of men beyond the age of sixty have some increase in the volume of the prostate and quotes various authorities as claiming that 5 to 14 per cent of these enlarged glands undergo malignant transformation (7). In view of these findings, the importance of early operation in prostatic hypertrophy is obvious if we are to forestall the development of cancer. Young is said by Creevy (6) to have found only 3.4 per cent of a series of 1,040 cases of prostatic cancer suitable for radical operation with hope of cure. Among 351 cases, Barringer (3) found only 4.5 per cent in which the cancer was localized to the prostate and periprostatic tissues. Bumpus (quoted by Creevy) discovered bone metastases in 24 per cent of his patients on the initial examination, and Ferguson (8) stated that 30 per cent of his patients came to him with metastatic lesions.

These facts are mentioned in explanation of the high percentage of failures in the treatment of prostatic cancer. Charles Mayo is quoted (11) as saying that, whatever one does, prostatic cancer is incurable, an aphorism which may require some modification in view of the more recent work of Huggins and others (1, 2, 15, 17).

Reports on the use of radiation in the treatment of prostatic cancer have long appeared in the literature. Bumpus, in 1922, reported a series of 217 cases treated with radium applications, but only 8 of this number were alive after three years (5). In 1942, Barringer (4) reported a series of 352 cases treated by some form of irradiation—chiefly implantation of radium needles through the perineum or suprapubically—with a minimum of surgical intervention. Thirty-six (10 per cent) of the patients survived more than five years. Of these, 15 died of carcinoma between the fifth and tenth year, while 21 (6 per cent of the total) were alive and apparently free from cancer after five to nineteen years. In 2 cases (proved by biopsy) coming to necropsy six and seven years, respectively, after treatment, no trace of cancer was found.

Thompson (19) believed that complete surgical removal of even the smallest prostatic cancer is impossible because of its early invasive growth (Kahler, Baron, and August). At the Mayo Clinic, from which his report comes, suspicious nodules are irradiated and kept under observation. When obstruction occurs, transurethral resection is done in addition to irradiation or orchiectomy. Of 877 patients surviving operation (among a total of 887), 206 received irradiation, chiefly by 200-kv. roentgen rays. Five-year results were available for only 69 of these patients (treated prior to 1937). Of these, 14.5 per cent were still alive.

The question arises: How can radiation act on a carcinoma composed of such highly differentiated cells as are found in these prostatic neoplasms? In the case of radium implantation, this is easily explained by the cauterizing action of the alpha and

beta particles, leading eventually to fibrosis. In the case of roentgen therapy and distance irradiation from a radium bomb or radium pack, the explanation lies in the fact that so many of these carcinomas develop in hypertrophied glands with an abundant, well vascularized stroma, which responds favorably to irradiation. In the alveolar type of cancer, the alveoli are closed and conglomerated.

Krompecher, according to Ewing (7), included among prostatic neoplasms adenocarcinomas containing basal cells, which are known to be radiosensitive. Herzog (9), quoted above, found that 25 per cent of his cases were a combination of adenocarcinoma and solid undifferentiated carcinoma. There may also be pavement cells in neoplasms arising from the urethral canal in the glands about the bladder neck (called by Coutts "feminoides"), which are not cured by estrogens but do respond to irradiation. Finally, Kaufmann (quoted by Ewing) has described round-cell sarcomas of the prostate. Munger (14) has covered the situation in a general way in the statement that, while most malignant prostatic tumors are adenocarcinomas, and consequently radioresistant, it is noteworthy, nevertheless, that they are decidedly more radiosensitive than the same type of tumor in the digestive tract.

Young (22), in 1913, inspired by the work of Pasteau and deGrais, conceived the idea of a radium-bearing sound for insertion into the urethra. He cited the work of Deming, who demonstrated conspicuous absorption and destruction of cancer tissue following the implantation of radium needles through the perineum or urethra and mentioned a case in which so great reduction in the size of the tumor was effected that radical operation became possible and the patient was well eleven years later. "This fortuitous case," wrote Young, "would seem to indicate that radium should be employed more frequently in an effort to make some of these cancers curable by the radical operation." I myself presented before the Sociedad de Cirugía of Santiago, Chile, in person, a patient who had been treated by perineal implantation of radium needles sixteen years earlier. Young mentions briefly roentgen therapy as being effective in some cases of extensive carcinoma.

The more recent use of radiation in carcinoma of the prostate has been in association with orchiectomy or roentgen castration, as mentioned above.

CASE REPORTS

CASE I: A. M., age 56, was operated upon in May 1928 by Dr. Coutts for cancer of the prostate. A nodule about the size of a hazelnut, invading the right lobe and involving the seminal vesicle on that side, could not be removed. The histologic diagnosis was alveolar adenocarcinoma.

Following operation, hematuria and frequency continued, and examination in September 1928 showed invasion of the right half of the pelvis. On Sept. 12, radium therapy was begun. Five long needles of 1.33 mg. each, with 0.5 mm. Pt and 1.0 mm. brass filtration, were implanted through the perineum into the nodule surrounding it and left for five days for a dose of 6.25 mcd. (831 mg. hr.). On the day of their removal, a radium pack (six 10-mg. tubes with 2.0 mm. Pt filtration) was applied to the hypogastric region at 4.0 cm. distance from the skin and left in place for fifteen days, completing a dose of 162 mcd. (21,546 mg. hr.).

By Oct. 15, the urethral obstruction, hematuria, and frequency had disappeared, the affected lobule had flattened, and the patient was able to sleep from 11 P.M. to 5 A.M. without urinating. The only complaint was sexual impotence. There was no further change until the beginning of 1931, when the condition suddenly became worse and death from recurrence ensued.

Comment: In this case life was prolonged in comfort for more than two years. Besides the local action of the radium implanted in and around the mass, there was irradiation of the pubic region, since it is difficult to filter adequately a mass of 60 mg. of radium. Thus, unintentionally, the testes were irradiated with gamma rays in accordance with the procedure more recently recommended by Munger.

CASE II: A. D., age 60, was seen by Drs. J. L. Bisquertt and Correa in November 1929 with a hard, nodular, inoperable tumor of the prostate adherent to the rectum, diagnosed clinically as cancer. The patient had had a right orchitis of unknown origin in October 1928; in March 1929 he began to experience difficulty in urination and nocturia, and in May of that year retention occurred.

Eleven radium needles were implanted through the perineum: 9 of 40 mm. length, containing 2.66 mg. each, giving 4.32 mcd., and 2 containing 1.33 mg., giving 0.48 mcd. daily. The fact that the needles were arranged in the form of a tetrahedron 1 cm. apart, indicates the enormous size of the tumor. They were left in place for seven days, giving a total dose of 33.60 mcd., or 4,468.8 mg. hr.

On removal of the needles, the ligneous mass had become soft and was greatly reduced in size, so that treatment with the radium pack was omitted. All symptoms disappeared within a month and the patient was well seventeen years later.

Comment: While no histologic proof of cancer was obtained in this case, the experience of the urologists making the original examination was such that a clinical diagnosis can be accepted as reasonably conclusive.[2] In any event, a patient suffering from serious urinary disturbances obtained relief without operation and was still well after seventeen years. In view of such a result, failure to give radium therapy to advanced prostatic lesions, whether benign or malignant, is a serious omission.

CASE III: J. V. V., age 70, complained of urinary disturbances beginning in April 1929 and increasing in severity until retention occurred in March 1930. Because of severe back pain over a period of six months, he had been treated for lumbago. In April 1930, examination by Dr. J. Díaz Muñoz revealed an inoperable prostatic growth, the size of a man's fist. On May 3, six radium needles were implanted in the neoplastic tissue, by way of the perineum, giving a dose of 17.28 mcd., or 2,298 mg. hr. in six days, at the end of which time they were removed. From May 12 to May 14, a radium pack was applied to the hypogastric region for a dose of 12.6 mcd. daily. The patient stood the treatment poorly however, and it had to be discontinued. He left the hospital on May 17, at which time urination was easy. Unfortunately cachexia ensued; roentgen radiation could not be given for the severe lumbar pain, and death ensued from bone metastases in September 1930.

Comment: While dysuria was relieved in this case, treatment could not be completed with roentgen rays, and generalization of the neoplastic process was not halted. Orchiectomy or irradiation of the testes might have proved useful.

[2] Dr. Gonzales Rioseco, at the Sixth Surgical Congress, held in Concepción in May 1946, said: "Rectal touch practised by an experienced specialist gives the necessary data for diagnosis." I believe that he is right.

CASE IV: E. R., age 59, complained of dysuria, retention, and severe pain suggestive of lumbago. He was examined by Drs. Díaz Muñoz and Kuschel, who found a greatly enlarged prostate and carcinoma. Cystostomy showed the growth to be even more extensive than it appeared clinically and confirmed the impression of inoperability. Vesical drainage was established, and fifteen days later eight needles of 2.66 mg. of radium each (40 mm. length, 0.5 mm. Pt filter) were implanted through the perineum, being permitted to remain for six days, for a dose of 23.04 mcd., or 3,064 mg. hr. Treatment was well tolerated and dysuria was promptly relieved. The spinal metastases were not treated, and the patient died a year and a half later from generalization of the disease.

Comment: In this case dysuria was relieved and the patient felt well enough that he did not wish to be treated for what he designated as his bearable lumbago. The final histologic diagnosis (Dr. Croizet) was adenocarcinoma.

CASE V: G. C. D., age 59, was seen by Dr. Díaz Muñoz in October 1929 with a hard, ligneous pelvic-prostatic mass diagnosed as carcinoma. He gave a history of dysuria since August 1929, culminating in retention. Only in June 1930, however, after repeated episodes of hematuria, was treatment accepted. At that time, six 40-mm. needles, each containing 2.66 mg. of radium, with 0.5 mm. Pt filtration, were implanted in the mass through a perineal incision, being left for a dose of 23.03 mcd., or 3,044 mg. hr. Because of the severe hematuria and the presence of urethral nodules, a radium needle (2.66 mg.) in a small catheter was introduced into the urethra for seventy-two hours, giving a total dose of 1.44 mcd., or 191.52 mg. hr., over a length of 40 mm., a very small intra-urethral dose. One month later urination occurred for the first time without catheterization, the prostate began to decrease in size and hardness, and there was a gain of 5 kilos in weight. The patient then left to recuperate in the country and was not again seen until two years and two months later, when he returned with a mass in the left ilio-inguinal region, which was believed to be of the same nature as the original prostatic tumor. The prostate was found on rectal palpation to be in good condition. Irradiation of the inguinal mass (5,100 r) was carried out from Aug. 23 to Sept. 7, 1932. An immediate weight increase (from 59 to 63 kilos) ensued, but in December the patient's condition became worse, and death occurred early the following year.

Comment: Biopsy in this case showed adenocarcinoma. In spite of the desperate condition of the patient when treatment was instituted, a substantial improvement

was obtained for a period of two and a half years, which compares favorably with the results of the treatment now in vogue. It is of interest that the patient's wife was seen in 1934 with a squamous-cell epithelioma of the urethra, which is being treated by radium.

CASE VI: L. A. M., age 50, had an indurated, ligneous, irregular prostate the size of an orange. He gave a history of dysuria since 1929, culminating in sudden retention following a heavy meal and excessive drinking. The patient had been under the care of two specialists and had undergone bladder irrigations. According to his statement, he became worse on one occasion following this procedure and a month later expelled a mass of hair.[3] On Feb. 23, 1931, eight radium needles, 40 mm. long, of 2.66 mg. each with 0.5 mm. Pt filtration, were implanted through a perineal incision—four in each lobe of the prostate. A dose of 30.72 mcd., or 4,085.76 mg. hr., was given in eight days. This treatment was well tolerated but the patient would not consent to further irradiation with the radium pack or roentgen rays. The mass in the prostate diminished in size, but pain and tenesmus continued, cachexia developed, and death occurred in 1931.

Comment: This is the only case in which some relief of vesical complaints was not obtained. We explained this failure on the hypothesis that the tumor was a radioresistant teratoma.

CASE VII: J. C. G., age 68, was seen in July 1928 in Professor Bisquertt's clinic with cancer of the prostate, proved by biopsy. The gland was the size of an orange, ligneous, indurated, and irregular. Eight 2.66-mg. needles were implanted for seven days, giving a total dose of 26.88 mcd., or 3,575 mg. hr. Dysuria was relieved and the patient was well up to June 1931. At that time the prostate was reduced in size but a tumor had appeared in the left iliac fossa and there was severe pain in the sacrum radiating toward the left thigh. The patient was also suffering from diabetes. Roentgen therapy was advised but refused, cachexia developed, and death ensued in December 1931.

Comment: This is another example of three-year survival in relatively good health. As in other cases, by means of a simple procedure almost as much was accomplished as could have been achieved by orchiectomy, without the production of emotional or mental disturbance.

CASE VIII: D. B., age 64, had been quite well until March 1932, when, following coitus, he noticed blood on the meatus. Subsequently hematuria occurred and on examination a hard, irregular prostatic growth was discovered, which had already extended beyond the capsule. As the tumor was considered inoperable, suprapubic cystostomy and perineotomy were done, as in Case IV (a procedure described as recently as 1936 by Chauvin). Four 40-mm. radium needles of 2.66 mg., 0.5 mm. Pt filter, were implanted in the prostate and one, in a catheter, in the urethra. Seven days later the needles were removed, having delivered a dose of 13.44 mcd., or 1,787.52 mg. hr., to the tumor and 3.36 mcd., or 446 mg. hr., in the urethra. A week later the cystostomy was closed, a catheter being left in place for three days longer. Hematuria ceased. Roentgen therapy was then given—4,200 r in twelve sessions (June 1932). The patient remained in good condition, with no impairment of sexual potency, until June 1942, when severe pelvic pain developed. Castration and transurethral resection were then done by Dr. Bernardo Lira without affording relief. I saw the patient in January 1943 in very poor condition. Roentgen irradiation of the lumber spine and sacroiliac region was without effect and death occurred a month later.

Comment: This patient, with a carcinoma of the prostate, proved histologically, lived for ten years in good condition. We do not believe that an equally good result could have been obtained with castration and estrogen therapy.

CASE IX: Dr. D. gave a history of dysuria and lumbar and sacroiliac pain. His prostate was enormously enlarged, indurated, and ligneous to the touch. He would not permit implantation of radium needles, and roentgen therapy was instituted. After ten treatments, during which a total dose of not more than 2,500 r was given, further irradiation was refused and death from cachexia ensued a few months later.

Comment: In this connection, it may be said that physicians frequently believe that it is the same thing to apply 1,000 r and 8,000 r, for example, and that treatment is the same for all cases. They fail to appreciate that radiotherapy, like such drugs as penicillin and the sulfonamides, must be given in appropriate dosage and at suitable intervals.

CASE X: G. R. C., age 64, was seen in 1934 complaining of dysuria. Examination by Dr. Díaz

[3] This suggested to me the possibility of a dermoid cyst. Ewing, discussing dermoid cysts of the pelvic connective tissues, wrote: "The presence of hair in the evacuation has been the first symptom observed, or the bladder can be invaded and hairs can appear in the urine."

Muñoz and Dr. Donoso Barthet revealed a prostatic-pelvic carcinosis. A course of irradiation—7,000 r—was given to the pelvis from May 15 to June 20, through six fields. The patient felt much improved until October, when a phlebitis of the left leg developed with severe pain in the lumbar region. "Cobrina" was injected without effect. Death from cancer ensued in November.

Comment: This case is an example of a far advanced lesion of a high degree of malignancy. Relief of dysuria was of only four months' duration.

CASE XI: A. C., age 63, had experienced urinary obstruction since April 1935. In October of that year he consulted Professor Bisquertt, who on examination discovered an indurated, ligneous mass shaped like the head of an ox, with the seminal vesicles forming the horns. Cystostomy was done and radium was implanted transperineally—seven needles of the type previously described—for a dose of 26.88 mcd., or 3,575 mg. hr., over eight days. By December the prostatic mass had disappeared except for slight induration of the left vesicle. Failure of the cystostomy to close led the patient to refuse further treatment with roentgen rays; the left vesicle continued to increase in size and, in spite of palliative measures, death occurred in January 1937. Biopsy showed adenocarcinoma.

Comment: The vesical disturbances having been relieved in this case and the prostate greatly reduced in size, I believe external irradiation, as in Case I, might have been useful.

CASE XII: C. A. B., age 70, was operated upon in June 1934 by Dr. Coutts for carcinoma of the prostate. Extirpation was impossible, however, as the entire capsule was invaded and indurated. Dysuria, which had been present since the end of 1933, went on to obstruction. The patient was again examined in May 1935, when an indurated mass the size of an orange was present. Hematuria had also appeared. Irradiation to the hypogastrium was begun on May 6, 1935, with a radium pack[4] consisting of ten 10-mg. tubes at 5 cm. from the skin. A dose of 180 mcd., or 23,940 mg. hr., was given in ten days. The urinary output increased from 800 to 2,500 c.c. daily, and the patient, previously prostrated, was able to be up. During July he received additional radiation to the pelvis—5,000 r. He continued to feel well till January 1936, when severe pain in the spine developed. There was no recurrence of dysuria, but spinal metastases had evidently occurred, and death followed in March 1936. The biopsy diagnosis was adenocarcinoma.

[4] Columbia paste (Esguerra; Regaud; Monod; Lacassagne).

CASE XIII: A. H., age 78, was operated on for prostatic adenocarcinoma, proved histologically, on June 26, 1931. In January 1936, hematuria and urinary difficulties developed. At that time, an indurated prostatic mass, 7 cm. in diameter, was found, and indurated seminal vesicles were also palpated. From March 3 to April 17, 8,000 r were delivered to the pelvis. The mass was greatly reduced in size, hematuria ceased, and the patient's general condition improved. He was followed for two and a half years.

Comment: X-rays in sufficient dosage served to keep this patient well for at least two and a half years. Undoubtedly the testes received some radiation, which may have contributed to the good result.

CASE XIV: W. E., age 60, was seen about the middle of 1937 complaining of impotence, constipation, and loss of weight (15 kilos) but *not of dysuria*. In the right iliac fossa was a ligneous indurated mass the size of a fist. Routine examination revealed, also, a hard prostate, about the same size. Suspecting a prostatic lesion, I sent the patient to Professor Bisquerrt, who made a clinical diagnosis of prostatic carcinoma, with invasion of the hypogastric and iliac lymph nodes. Roentgen therapy was given from Sept. 27 to Oct. 10—8,000 r through three 10 × 10 cm. fields to the abdomino-iliac mass and an equal amount through five fields to the region of the prostate. The factors, as in the other cases, were 200 kv., 10 ma., 2.0 mm. Cu filter, 80 cm. distance.

Following treatment the patient showed a remarkable improvement, working as he had never worked before as head of a large industry. He remained well for two years. In July 1939 he was again examined. The prostatic and abdominal masses had disappeared, and there had been an increase of 16 kilos in weight, but there was evidence of spinal metastasis. Roentgen therapy to the spine was given for thirty days for a total dose of 3,500 r, liver extract being injected to avoid anemia. The pain was relieved and the patient returned to his work for another year. In October 1940 tetraplegia developed and there was evidence of osteoblastic metastases even in the cervical spine. Roentgen irradiation afforded slight palliation but cachexia supervened, with death in January 1941.

Comment: In this case we have an example of prostatic cancer without urinary symptoms. The patient lived three years in excellent condition, able to carry on his work. The question arises as to what effect the radiation had upon the gonads. I believe that it exerted some effect, since the patient remained impotent after his

first treatment. No biopsy was done in this case.

Incidentally, the wife of this patient was seen in 1943 with a pavement-cell epithelioma of the cervix. She is now (1947) without evidence of cancer following radium therapy (Regaud method).

CASE XV: U. B., age 69, gave a history of urinary difficulties since the age of forty, becoming worse in the last two years. On examination, Professor Bisquerrt found an indurated prostatic mass invading the seminal vesicles. The clinical diagnosis was prostatic cancer arising in an old adenoma. No biopsy was done. As the condition was regarded as inoperable, x-ray therapy was given in July 1939—8,000 r in 30 sessions, with the factors described in the cases recorded above. After a month the urinary symptoms disappeared. The patient's general condition improved, and he lived until 1943, when he was reported to have died of bronchopneumonia.

CASE XVI: C. M., age 74, was first seen by me in December 1939. He had been operated on in 1937 for prostatic carcinoma (proved histologically). Metastases were now present in the 4th cervical vertebra and the 6th left rib, and there was a local recurrence in the left half of the true pelvis. Roentgen therapy was given to the metastases and pain disappeared. Only 3,500 r were given to the pelvis, as we feared to use a larger dose because of the possibility of anemia, in view of the patient's age and the fact that the short bones had been irradiated. After eight months of well-being, death occurred from pneumonia.

Comment: In spite of the relief following treatment, I believe that the local recurrence in this instance continued to progress. This would have been an appropriate case for orchiectomy.

CASE XVII: F. W., age 76, was seen by us in August 1940, with a history of dysuria for five years, becoming more severe in the past six months, with loss of weight and pelvic pain. He had undergone section of both spermatic cords in 1934 for a bilateral recurrent epididymitis. At that time there were 300 c.c. of residual urine. Professor Bisquerrt found a large irregular prostate, fixed by ligneous adhesions. As the condition was regarded as inoperable, deep roentgen therapy was given—4,500 r in 18 sessions. Improvement followed and plans were made for the implantation of radium through the perineum. Unfortunately an indiscreet relative told the patient that he was suffering from cancer and he committed suicide.

Comment: This tragic case carries its own lesson. In our Institute we never speak of cancer. My patients know that I am a specialist in that disease, but so long as there is any doubt of its presence they remain hopeful and give us the co-operation that is so necessary.

CASE XVIII: G. Q., age 55, had suffered from hematuria and dysuria in 1934. He was examined in July 1941 by Professor Bisquerrt, who found a greatly hypertrophied prostate with indurated nodules and invasion of the left vesicle. A perineotomy was done on Aug. 21, 1941, and radium needles were inserted for a dose of 20.16 mcd., or 2,681 mg. hr., in seven days. As we were not sure that adequate radiation had been delivered to the seminal vesicles, roentgen therapy was given to the pelvis—5,000 r. The patient was followed for two years. The biopsy diagnosis was adenocarcinoma and prostatic hypertrophy.

CASE XIX: J. D. C., age 76, had suffered from progressive dysuria since the end of 1940. The prostate was large and indurated. Perineotomy was done on Aug. 28, 1941, and six radium needles were implanted, being left in place for nine days, giving a dose of 25.92 mcd., or 3,447 mg. hr. Dysuria was relieved and when the patient was examined two years and nine months later, he was quite well. The biopsy diagnosis was adenocarcinoma.

CASE XX: J. L., age 66, suffered from dysuria from the beginning of 1941. Examination revealed a large, indurated, inoperable prostate. Seven radium needles (2.66 mg.) were implanted in the prostate transperineally and left in place from Dec. 23 to Dec. 31, 1941, for a dose of 26.88 mcd., or 3,575 mg. hr. Urinary symptoms disappeared until May 1945, when the prostate again increased in size and retention developed. Roentgen therapy to the pelvis, including the gonads, was then given, 7,000 r being delivered through six fields in thirty sessions. Fifteen days later catheterization was no longer necessary. The biopsy diagnosis was adenocarcinoma.

CASE XXI: S. C., age 70, gave a history of dysuria for the past year. The prostate was large, indurated, ligneous, and inoperable. Radium was implanted (Feb. 19–23, 1943) as in the previous case, and a month later catheterization was unnecessary. This patient was followed for only six months. The histologic diagnosis was adenocarcinoma.

CASE XXII: F. N., age 78, had dysuria and retention for about a year. Operation could not be undertaken because of the advanced age and poor general condition. Roentgen therapy was given, including the gonads, but when the patient was last heard from retention was still present.

CASE XXIII: M. B., age 71, consulted Professor Lobo-Onell because of dysuria. The prostate was

large and indurated. As the condition was inoperable, roentgen therapy—7,000 r—was given to the pelvis in 1939. After a year and a half, during which the patient remained in good condition, he returned with a recurrence. Roentgen therapy was again given—4,500 r, and in February 1943 a third series was given for a further recurrence. The patient remains well. There was no biopsy in this case, but the clinical diagnosis is considered reliable.

CASE XXIV: C. D., age 53, suffered from dysuria from 1941. In December 1942, episodes of massive hematuria occurred at the beginning and end of micturition. Examination in 1943 by Professor Bisquertt revealed a large, indurated, irregular prostate. Cystoscopy showed small bleeding outgrowths on the bladder neck. There had been a loss of 6 kilos in weight. Estrogens were without effect and I therefore undertook to irradiate the lesion and the testicles (July 3–Aug. 15, 1943). Dysuria at first became worse but began to improve during the fourth week of treatment, hematuria ceased, and the prostatic mass disappeared. There was a gain in weight of 14 kilos. In the last two years acid phosphatase determinations on two occasions have been normal.

CASE XXV: D. H., age 62, underwent transurethral resection in 1943. He remained well until April 1945, when hematuria and dysuria recurred and his general condition declined. I attempted to irradiate the testicles and prostate in June 1945, but the patient was extremely nervous and toxic so that no regularity of treatment could be observed. Only 2,000 r were given. The condition failed to improve and death occurred from cancer.

SUMMARY OF CASES

We have here 25 cases of cancer of the prostate, of which 14 (I, IV, V, VII, VIII, XI, XII, XIII, XVI, XVIII, XIX, XX, XXI, XXV) were proved histologically, while the others gave undoubted clinical evidence of malignant growth. Case VI was presumably a pelvic dermoid cyst. With this one exception, every patient receiving adequate radiation experienced prompt relief of dysuria for varying periods. In each instance there was marked diuresis following treatment.

One patient (Case II) has lived seventeen years in good condition, *i.e.*, six years longer than the patient mentioned by Young (22). A survival period of ten years was obtained in Case VIII. In Case XV death from bronchopneumonia occurred four years after relief of dysuria by roentgen therapy. In Case XXIII the survival period has reached five and a half years with recurrences at a year and a half and again two years later. The patient is without urinary symptoms at the time of this report. Still another patient (Case XX) is without symptoms three years and ten months after the first treatment, a recurrence having been treated in the interval by irradiation to the pelvis.

In 5 other cases (I, V, XIII, XIV, XXIV) dysuria was relieved for periods from two and a half years to over three years. In Case XVIII relief from dysuria had continued for two years when the patient was last heard from, and in Case XII dysuria disappeared for ten months. Briefer periods of relief were obtained in the remaining cases, in which complete treatment could not be given.

CONCLUSIONS

We are in agreement with Barringer that treatment of prostatic carcinoma with radiation will relieve dysuria and prolong life in comfort. We believe that the results compare favorably with those of transurethral resection, which was reported by Thompson and Emmett (20) as giving 74 per cent of one-year survivals in a series of 253 cases; 46 per cent two-year survivals, 31 per cent three-year survivals, 17 per cent four-year survivals, and 8.7 per cent five-year survivals.

We believe that before instituting treatment for any case of prostatic carcinoma, the method of choice for that case should be determined, whether transurethral resection, irradiation, or castration with or without estrogens, or some combination of these procedures.

We believe irradiation is most useful in reducing the volume of the primary tumor and relieving pain due to metastases. If estrogens and castration fail, as they may in tumors arising in the periurethral glands, radiation can still be employed.

We agree with Munger that adequate testicular and regional irradiation diminishes hormone production (by regional

irradiation we mean irradiation to the lumbo-aortic and suprarenal regions).

We believe that irradiation should be given not only to the testes and the pelvis, but to the suprarenals and hypophysis to eliminate all extragonadal sources of androgen.

Finally, we believe that nothing takes the place of early diagnosis, permitting radical operation without undue risk.

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SUMARIO

Cáncer de la Próstata

Veinticinco casos de cáncer prostático fueron tratados por medio de la irradiación (principalmente en forma de radio por vía intersticial, con o sin irradiación externa con compresas de radio o rayos X). Con la sola excepción de un enfermo en que se creyó había un quiste dermoideo, todos los que recibieron tratamiento adecuado obtuvieron rápido alivio de la disuria. Un enfermo vivió 19 años en buen estado; otro 10 años y otro cinco años y medio, durante los cuales tuvo dos recurrencias que exigieron nueva irradiación. Un enfermo falleció de bronconeumonía cuatro años después del alivio de la disuria, y otro estaba sin síntomas tres años y medio después, habiendo entre tanto recibido irradiación con motivo de una recurrencia. En 5 casos hubo alivio de la disuria durant dos años y medio a tres años, obteniéndose alivios más breves en los casos restantes.

De lo anterior dedúcese que el tratamiento del cáncer prostático con la irradiación aliviará la disuria y prolongará la vida en comodidad, comparándose favorablemente el resultado con el obtenido con la resección transuretral; que la irradiación es de la mayor utilidad para reducir el volumen del tumor primario y aliviar el dolor debido a las metástasis; que la adecuada irradiación testicular y regional es útil para mermar la hormonogenia; y por fin, que nada suplanta al diagnóstico temprano, que permite llevar a cabo la operación radical sin correr demasiado riesgo.

Application of Radioactive Isotopes to the Study of Radiation Effects in Cells

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NOTABLE AMONG the fundamental contributions due largely to the availability of tracer isotopes is the concept of the dynamic state of cellular constituents. The structural and metabolic components of the cell are involved in a constant flux of rapid reactions, as shown so convincingly by Schoenheimer (1) and others. Biochemical entities such as proteins, fats, and carbohydrates are linked by simultaneous anabolic and catabolic processes through a "pool" of relatively small atomic groupings which originate from no particular source but are contributed by all cellular materials, structural or otherwise. Despite this seeming welter of reactions, regulation mechanisms in normal metabolism are so efficient that cells and organs remain constant in total amount and composition. Cellular dysfunction and disease processes involve disturbances in these regulation mechanisms. That the chemical nature of these mechanisms has remained obscure is due in no small measure to the lack of a technic for following the exchange of reactive atomic groupings in systems which exhibit no over-all changes in chemical composition. It is in the study of regulation mechanisms in such systems that labeling technics utilizing tracer isotopes can be expected to make many important contributions. It follows that research into changes in cell metabolism brought about by absorption of radiant energy will be expedited and enriched by knowledge gained with such technics.

The responses of living cells to radiation are as diverse as the cells themselves. Photosynthetic organisms are so adapted to radiation that they prefer it for efficient cellular synthesis. From this extreme, the known complex of living systems exhibits responses less and less beneficial until the extreme of lethality is reached. It is evident that before a full understanding of radiation effects is possible it is essential to know in detail (*a*) the nature of the anabolic synthetic processes obtaining in the absence of radiation, (*b*) the nature of the foreign constituents introduced by irradiation of the cellular nucleus and cytoplasm, (*c*) the interaction of these foreign constituents in terms of competitive interaction with the normal metabolites for synthetic material. In this paper there will be reviewed a few researches which appear to be significant in that they suggest one kind of approach to these problems.

Hevesy and his co-workers (2) have applied radioactive phosphorus (P^{32}) in studying the effect of x-rays on cellular division. The particular advantage of using the tracer isotope in these investigations is that there is afforded a means of investigating changes in tissues which have reached full growth. The usual method of mitotic counts is applicable only to growing tissue. A convenient direct method for ascertaining cellular responses or change in metabolic turnover in full-grown tissues is afforded by studying the rate of synthesis of desoxyribose-nucleic acid before and after irradiation. The basic importance of this moiety in cellular synthesis has been suggested by numerous investigators (Caspersson, 3; Brachet, 4; and others).

A specific example may be cited from the researches reported by von Euler and Hevesy (5). When labeled inorganic phosphate is administered to rats im-

[1] Presented at the Thirty-second Annual Meeting of the Radiological Society of North America, Chicago, Ill. Dec. 1–6, 1946.

TABLE I: RATIO OF NEWLY FORMED DESOXYRIBOSE NUCLEIC ACID PRESENT BEFORE AND AFTER IRRADIATION IN ORGANS OF YOUNG RATS. DOSE 2,000–2,250 r (AFTER HEVESY)

(*Time of Experiment: 2 hours*)

Organ	P^{32} Administered After Irradiation	Irradiated Throughout Experiment
Liver	2.3	11
Spleen	...	5.3

planted with Jensen's sarcoma, it is found that the labeled phosphate enters the sarcoma fairly rapidly. In two hours the inorganic phosphorus of the sarcoma is found to contain nearly the same amount of labeled phosphorus as that in the circulating plasma phosphate. Thus the specific activity which gives the amount of P^{32} per milligram of total phosphorus is roughly the same in these two fractions after a lapse of a few hours. It is known from tracer studies that the phosphate bound in nucleic acid and nucleoprotein cannot interchange with inorganic phosphate as such but can make its appearance in nucleic acid only by actual synthesis into the nucleotide. Consequently, the appearance of labeled phosphorus in the nucleic acid fraction gives an index of newly synthesized nucleic acid. The ratio of the specific activities of cellular nucleic acid and plasma phosphate reveal the percentage of nucleic acid synthesized during the interval between administration of the labeled phosphate and the end of the experiment. This synthesis in Jensen rat sarcoma corresponds to an average of about 2 to 3 per cent in two hours. X-ray irradiation of the sarcoma reduces the synthetic activity markedly as compared with the normal rate. More important is the observation that inhibition of synthesis is less marked when studies are conducted with labeled phosphate administered sometime after irradiation. Thus, when labeled phosphate is injected during irradiation lasting two and one-half hours, the total dosage being 2,250 r, the synthesis of desoxyribosenucleic acid is diminished to one-seventh of the normal value, whereas if the labeled phosphate is administered a short time after irradiation, the normal rate is decreased only by about one-half.

In normal tissue much the same effects are observed. In Table I, taken from Hevesy's paper (2), there are shown data on the ratio of newly formed desoxyribosenucleic acid in the organs of young rats before and after irradiation. It is seen that when the rat is exposed to x-rays throughout the experiment there results a greater inhibition of nucleic acid synthesis. These data are obtained with rapidly growing animals. In the liver and spleen of adult rats, the synthesis of nucleic acid is found to be many times smaller than in the corresponding organs of young rats, as would be expected. However, the x-ray inhibition of nucleic acid formation is about the same whether the tissues are growing actively or not. The inhibitory effects of x-rays as evidenced by nucleic acid formation are much less pronounced if, instead of sacrificing the animal immediately after irradiation, the inhibition is observed several hours after the termination of irradiation. The experiments of Hevesy and his coworkers indicate that about 75 per cent of the x-ray inhibition is counteracted in two hours after irradiation.

These results, particularly those involving the time factor, are consistent with the notion that there is an interaction of chemical agents produced by x-rays with the cellular constituents mediating protein synthesis and cellular growth. A striking experiment bearing on this point may be cited from the work of Ahlstrom, von Euler, and Hevesy (6). Rats were inoculated with two sarcomas, one of which was subjected to irradiation up to 2,000 r, the other being shielded. The two sarcomas on a single rat were connected only through the circulatory system of the animal. Nucleic acid formation, as evidenced by use of labeled phosphate, was inhibited in the shielded sarcoma almost as much as in the sarcoma irradiated directly. This indicates the production of a diffusible factor in tissue under irradiation which can influence unirradiated cells. The nature of this factor remains to be elucidated.

The work on nucleic acid turnover under conditions of irradiation is most suggestive when compared with work on various cellular processes modified by chemical agents. Most striking is the action of mustard gas and its nitrogen-containing analogues, the β-chlorethyl amines, on the structure and function of chromosomes (7). It has been shown that in *Drosophila melanogaster*, exposure of adult male flies to sublethal doses induces a high incidence of sex-linked lethals much in excess of the number to be expected on the basis of the natural mutation rate. Horowitz (8) and his co-workers, in confirming and extending the original observations of Auerbach (7) and others, have shown that the mustard gas-induced mutations are remarkably similar to those observed following x-ray irradiation.

Chemical effects may be associated with a range of energies up to 100 kilocalories, which is not far removed from the energies liberated by absorption of ultraviolet radiation (4–5 electron volts). X-rays release considerably more energy per unit of absorption, so that x-ray effects may be expected to introduce more intense dislocations of the cellular chemical pattern. On the other hand, the results obtained with the mustards indicate that both types of cellular disturbance may funnel into a common pathway. In this connection, it should be remarked that a link between the energy region of x-rays and chemical agents has been provided to some extent by the observation of Latarjet (9), who has shown that both ionization and molecular activation can induce the same chemical changes in the same sensitive cellular zone. The absorption of a given quantity of energy, whether delivered by x-ray photon or by many ultraviolet photons, leads to the same amount of cellular inactivation. In these experiments, Latarjet measured the energy required to produce such effects as the inactivation of bacteriophage, sterilization of dysentery bacillus, and the sterilization of yeast. It appears that the accumulation of energy as molecular activation delivered in small packets by ultraviolet photons can give the same effect as a single higher energy event (ionization) obtained by absorption of a single x-ray photon.

On the basis of these results it is not implausible that the induction of cellular dysfunctions such as cancers and leukemias may involve a common metabolic pathway whether the causative agent is radiation or a chemical It is important therefore to inquire into the normal mechanisms prevailing in the cell for protein synthesis, particularly as mediated by the enzymes present, the substrates they require, and the relation of these enzyme populations to the nuclear genes. Spiegelman (10) has summarized recently the evidence for a theory linking genes in the cellular nucleus with enzymes in cytoplasm through a bridge of self-duplicating nucleoprotein units to which the term "plasmagene" is applied. According to this theory, the genes in the nucleus continually produce replicas of themselves which are ejected into the cytoplasm. These units or "plasmagenes" are assumed to be nucleoprotein in nature and possess varying degrees of capacity for self-duplication. The plasmagenes determine the types and amounts of protein and enzymes synthesized, each plasmagene competing with the others for cellular protein. It is supposed that heritable changes in the ultimate cellular composition can be initiated and maintained by varying the substrate to which the plasmagenes are exposed. This concept of cytoplasmic inheritance interprets a process such as cancer as due possibly to a mutation in a plasmagene, resulting in a new plasmagene foreign to the cell. This plasmagene mutant is enabled to compete successfully for protein and thus interfere with the ultimate development of normal cellular function. Such a concept provides an explanation for the appearance of a sudden heritable change in somatic cells, a phenomenon which appears to be typical of the cancer process (11)

With such considerations in mind, an inquiry into the nature of the chemical processes involved in enzyme synthesis has been started by Dr. Spiegelman and

the writer. Some preliminary results using tracer phosphorus are of interest in connection with the problems which are discussed above.

Of necessity, the initial problem in enzyme synthesis must be that of the energy sources and substrates for the synthetic reactions. It will be recalled that in the normal anaerobic fermentation of glucose by yeast cells a portion of the glucose is assimilated into cell material. Inclusion of sodium azide in the medium in concentrations equal to 2.5×10^{-3} M., results in abolition of assimilatory activity, although the rate of fermentation is not affected. Under proper conditions, this chemical agent can inhibit a large variety of cellular functions involving synthesis, *i.e.*, enzymic adaptation, differentiation, ammonia assimilation, etc., although over-all rate of metabolic activity is not changed. From the fundamental and brilliant research of the Coris, Warburg, Meyerhof, Parnas, and others, it may be suspected that the action of azide on mobilization of phosphate for synthesis of organic phosphate esters as synthetic intermediates may be involved. Therefore, we have begun by comparing the distribution of phosphate in the various cellular fractions as influenced by synthetic activity. By the use of azide and tracer phosphorus (P^{32}), it has been possible to study the flow of phosphate between various cell fractions while cellular material is or is not being synthesized and while the over-all utilization of carbohydrate is maintained constant.

In the initial experiments, yeast cells were suspended in a medium containing P^{32} labeled inorganic phosphate. Samples of the cells were withdrawn at intervals during fermentation of glucose and analyzed chemically and by radioactive assay. A typical experiment gave results shown in Figure 1. In this experiment 2×10^{-3} M. NaN_3 was used. From the upper curve it can be seen that the azide did not affect the ability of the cells to metabolize glucose, since both the treated and untreated cells consumed glucose at the same rate. However, the control cells equilibrated organically bound phosphate rapidly whereas the azide treated cells did not. From this type of experiment it seemed reasonable to conclude that azide prevented the accumulation of organically bound phosphate. On the other hand, dinitrophenol, another agent capable of preventing synthesis while not inhibiting over-all utilization of glucose, did not interfere so markedly with formation of ester phosphate. The rate of equilibration of cellular phosphate with labeled inorganic phosphate was only 20 per cent less than the control in the presence of a concentration of dinitrophenol sufficient to inhibit synthesis of cellular material completely.

To elucidate these results, experiments were designed to obtain information on the transfer of phosphate between the various organic phosphate fractions of the cells while enzyme or protein synthesis was occurring. It was necessary to label the various fractions of the cells before the experiment so that subsequent movement of phosphorus from one fraction to another could be followed.

Cells were grown in the usual medium in the presence of P^{32} labeled inorganic phosphate. The various fractions of cellular phosphate were all labeled in this way. After forty-eight hours, the cells were harvested, washed free of contaminating labeled inorganic phosphate by successive rinses with unlabeled M./15 KH_2PO_4 solution, and resuspended in a medium containing unlabeled M./15 KH_2PO_4 and 4 per cent glucose. The carbohydrate was fermented under completely anaerobic conditions. During the process of fermentation there was no budding or increase in protein nitrogen.

It was found that within four hours one-half of the total activity was lost from the cells. Practically all of this loss could be accounted for in the acid-soluble fraction, constituting about 50 per cent of the total cell phosphate. The acid-insoluble fraction (presumed mainly nucleoprotein) had lost no activity; in fact, it had gained slightly in both total (P^{31}) content and in labeled

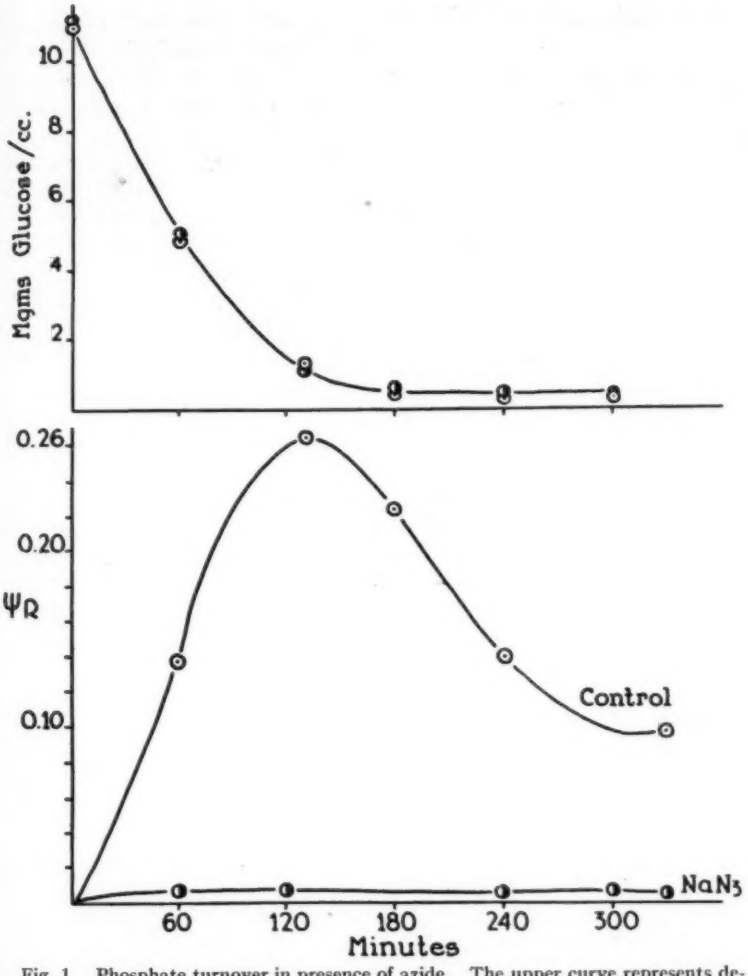

Fig. 1. Phosphate turnover in presence of azide. The upper curve represents decrease in glucose concentration of medium as function of time. It is seen that both azide-treated and control organisms ferment glucose at the same rate. In the lower curve the ratio of specific activities (P^{32}/P^{31}) in cell phosphate and extracellular phosphate is plotted against time. Equilibration is rapid in the control cells, reaching a maximum just before all glucose is exhausted, after which the ratio drops because of breakdown of newly synthesized intracellular organic phosphate and loss to medium. Little equilibration occurs in the presence of azide.

phosphorus, indicating some flow into this fraction. These data showed unambiguously that rapidly metabolizing but nondividing cells lost no phosphate from the "nucleoprotein" fraction even though there was a rapid equilibration of the remaining cellular phosphate.

The cells obtained from these experiments now contained a "nucleoprotein" fraction with a specific activity almost four times as great as the acid-soluble phosphate fraction. They therefore constituted good test material for further study of P-exchange between acid-soluble and "nucleoprotein" fractions. Long periods of fermentation (up to six hours) failed to change the total P^{32} content of the "nucleoprotein" fraction, although the specific P^{32} content declined somewhat owing to dilution by flow of low-specific activity phosphate from

the acid-soluble to the "nucleoprotein" fraction.

When the cells were induced to synthesize new protein by the addition of ammonia or by forcing the adaptive synthesis of a new enzyme, the "nucleoprotein" fraction exhibited a different behavior. Typical experimental results are shown in Figure 2. In this experiment cells were

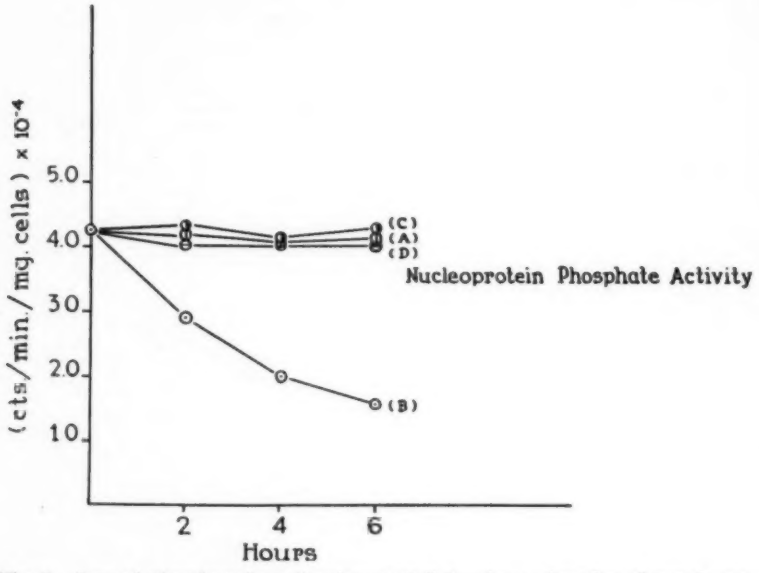

Fig. 2. Loss of phosphate from "nucleoprotein" fraction as function of protein synthesis. Symbols explained in text.

suspended in four different media: *i.e.*, (A) physiological saline and glucose; (B) physiological saline, glucose, and ammonium sulfate; (C) physiological saline, glucose, ammonium sulfate, and azide; (D) physiological saline, glucose, ammonium sulfate, and dinitrophenol. The concentrations of the azide and dinitrophenol were 5×10^{-3} and 5×10^{-4} M., respectively, so that enzyme synthesis was completely inhibited.

With glucose alone no change in P^{32} content was noted, whereas in the presence of ammonia the "nucleoprotein" P^{32} content fell to 38 per cent of its original value. It was found that both azide and dinitrophenol prevented this loss from the "nucleoprotein" fraction. When the cells were forced to adapt to ferment maltose, *i.e.*, form a new enzyme, a similar drop in "nucleoprotein" P^{32} content was observed.

These findings can be summarized as follows:

1. Metabolizing cells which are not actively synthesizing new protein do not transfer phosphate from the "nucleoprotein" fraction.
2. Synthesis of new protein or enzyme is associated with transfer of phosphate from the "nucleoprotein" fraction.
3. Agents which prevent enzyme formation and protein synthesis also stop flow of phosphate from the "nucleoprotein" fraction.

These results are in agreement with those of Caspersson in demonstrating a close connection between nucleic acid metabolism and protein synthesis. On the other hand, they extend those of Hevesy and his collaborators, since it is shown that not only the general turnover of phosphate but a continual supply of phosphate from nucleic acid is essential in maintaining

cellular synthesis and growth. It is also suggestive that phosphate-transferring enzymes in general have been found particularly easy to inactivate with mustard gas and its nitrogen-containing analogues (12). As remarked before, these agents exert nucleotoxic effects remarkably similar to those found to result from x-ray and ultraviolet irradiation.

It would be premature to suggest that disturbances in nucleoprotein metabolism are the central factor in induction of the pathological manifestations observed to result from irradiation of cells. This discussion is already replete with analogies and speculations. There does appear to be sufficient evidence available to indicate that investigation of cellular responses to a wide variety of chemical agents may clarify many aspects of the radiation problem, particularly in conjunction with isotope studies. The direct extension of researches, such as those cited on phosphate transfer, to studies of cells under irradiation can be expected to yield data of fundamental importance in the elucidation of radiation effects.

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DISCUSSION

(Papers by Quimby and McCune, page 201, and Kamen)

W. Edward Chamberlain, M.D. (Philadelphia, Penna.): Dr. Quimby always gives us a lesson in how to present a subject. I think probably everyone of you agrees with me in wishing that we could all present our material in such a clear, lucid way.

In a letter to me in advance of the meeting and in her remarks today, Dr. Quimby said something about her paper not being very important. I disagree with her on that point. It is important. It is very important to have meticulous studies and measurements of this sort, and the fact that the outcome was as had been expected, that in certain hypothyroid children the thyroid uptake was what could be anticipated from the work of Dr. Lawrence and Dr. Hamilton and from Dr. Quimby's own earlier work, doesn't lessen its importance. It is impossible, of course, to discuss that paper because nothing remains to be said.

A totally dissimilar paper is that of Dr. Kamen. It may be one of the most important papers that has ever been read at this Society, but I certainly feel that it is the kind of paper that we have to digest, that has to be read to be understood. In fact, Dr. Kamen probably doesn't realize how ill-prepared we radiologists are for understanding his essay. He kindly sent me an advance copy and I have worked at it very hard. As a result of my study I advise you to read it when it is published and to study it.

Papers of this sort really should be read by title and, when published, should be accompanied by a glossary of terms and perhaps some remarks by a co-author to bring it down to our level. A very stimulating part of the paper to me was that it opened up a little window, showing us that perhaps such a study can be tied in with some exciting work presented at the Westinghouse Forum in May by some of the biophysicists and biochemists. All of a sudden one of them got up on the platform and said, "What is a virus?" A virus may be one of the smallest particles of matter that can reproduce itself and, if so—and there is some reason to think it is so—it may be the same thing as a gene. Now I noticed that Dr. Kamen spoke of plasmagenes and described them as those molecules that reproduce themselves inside of nuclei and then find their way into cytoplasm.

I think one statement he made may well be the key to something important in our study of cancer. Suppose these protein molecules, the smallest molecules that are able to reproduce themselves, should be poisoned by some injury to the body and should begin to reproduce themselves in altered form (may be that is why cancer develops as a result of certain injuries); tie this up with Dr. Kamen's statement that these molecules are constantly reproducing themselves in large numbers in the nuclei and then finding their way into the cytoplasm; then recall the

possibility, suggested by someone else, that a virus may be the end result of a parasite which has lost all need for its cellular function except the function of reproduction; and finally consider the possibility that cancer is tied up with these reproducing molecules. I think you may see from this that a reading of Dr. Kamen's paper when it is published will be exciting and stimulating and that it may be a new approach to a vital problem.

Edith H. Quimby, Sc.D. (*closing*): I want to thank Dr. Chamberlain for his discussion, and I want to take issue with him on the subject of presenting fundamental scientific material in papers at our meetings.

I do not believe that such papers should be read by title. I think the essayist should make an attempt to recognize the limitations of a medical audience, and to a certain extent predigest the material for us, but I am afraid the radiologists in general will not read these articles in the journals unless they have been stimulated to do so. The best stimulation is a properly prepared report at a meeting, and I want to object strenuously to this audience being deprived of it.

However, I want to emphasize the matter of proper preparation. The essayist must consider his obligations to his audience and to his fellow speakers. The program has been prepared for a certain period, and each speaker knows his time allotment. His first duty is to prepare a version of his material which he can present within this time, and this does not mean a chopped-up version of the paper which is to be submitted for publication. It should mean a carefully prepared digest of it. If this must include the defining of new terms, well and good, but there should not be a mass of scientific detail. The full account will be published for study, and it will be studied if the presented paper is properly stimulating. In this connection I recommend that everyone who presents a paper at a meeting should read the editorial published on this subject by Dr. Golden in the *American Journal of Roentgenology* last April (1946).

Martin D. Kamen, Ph.D. (*closing*): I agree with Dr. Quimby, except that if I had spent my time in defining terms I would have been through only half of the glossary in twenty minutes. I have written a much more extensive article than I gave you. I worked very hard at this paper and I hope people will read it. Indeed, I am very anxious to have people read it because I want to find out what is wrong with it. Incidentally, I entertained an unfortunate misconception of the time allowed for its presentation.

There is another thing to be said about the unfortunate chemist thrown into this melange You will have to understand—and you will understand this quite clearly—that when you write an article for another group of people you are still aware that your own colleagues are looking at you and you cannot afford to be extremely labored about terms with which they are familiar. They will wonder why you are being so painfully clear. Usually in the hospitals they turn these articles over to biochemists or biologists to read. The result is that you may be looked at askance, and some of us are sensitive about that.

SUMARIO

Los Isotopos Radioactivos en el Estudio de los Efectos de la Radiación

Al discutir la aplicación de los isotopos radioactivos al estudio de los efectos de la radiación sobre las células, repásase también la labor de otros investigadores. El trabajo actual contiene el informe preliminar acerca de la naturaleza de los procesos químicos que intervienen en la síntesis de las encimas. Mediante el empleo del fósforo como localizador, se descubrió que: (1) las células metabolizantes que no sintetizan activamente nueva proteína no transfieren fosfatos de la fracción "núcleoproteínica"; (2) la síntesis de nueva proteína o encima se enlaza con la transferencia de fosfatos de la fracción "núcleoproteínica"; (3) los agentes que impiden la encimogenia y la síntesis de proteína también suspenden el paso de fosfatos de la fracción "núcleoproteínica".

Aunque sería prematuro indicar que los trastornos del metabolismo núcleoproteínico constituyen el factor central en la inducción de las manifestaciones patológicas derivadas de la irradiación de las células, parece que los datos disponibles y bastan para indicar que la investigación de las reacciones celulares a una amplia variedad de agentes químicos puede esclarecer muchas fases del problema de la radiación, en particular conjuntamente con los estudios de los isotopos.

Hemangioendothelioma: A Rare Malignant Tumor[1]

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New York, N. Y.

STOUT (10), Pack (6), and others have stated that hemangioendothelioma is a rare tumor. It is that belief that has led investigators to record their findings even in single cases (2, 3, 6, 7, 9) and has prompted the writer to offer the present report of an unusual example. The rarity of this tumor is substantiated by the fact that in the Department of Radiation Therapy at Bellevue Hospital, in a period of twenty-two years (1925–46), during which there were studied and treated many thousands of neoplasms, only 4 cases of hemangioendothelioma, pathologically confirmed, were observed. Through the courtesy of Dr. W. C. Von Glahn, director of the Department of Pathology, 4 additional cases were gathered from the various services of the hospital—an extremely low figure in view of the large number of surgical and pathological specimens seen yearly at this institution.

The unanimity of opinion that prevails as to the infrequency of this tumor does not exist however, when the question of its malignant character arises. Sweitzer and Winer (11) consider hemangioendothelioma as an angiomatous tumor of low-grade malignancy. Schwartz (9) describes it as a malignant vascular tumor which may run a benign clinical course. Baumann-Schenker (1) is somewhat less optimistic, for, of the 5 cases reported by him, 2 proved fatal within fifteen months of treatment; 1 patient was alive with metastases to the base of the skull; and the other 2 were alive and free of clinical evidence of the disease (less than three years after treatment). Stout declares that, although the growth may be rapid or slow, its high degree of malignancy can be judged by the fact that of his series of 18 patients, 10 had died with metastases, 1 had local persistence of the disease, 3 had not been followed, and 4 were known to be alive. In only 1 of these last 4 cases, however, had more than five years elapsed after the excision of the tumor.

ETIOLOGY

Much speculation has arisen as to the etiology of hemangioendothelioma. Hewer and Kemp (7), reporting a case of hemangioendothelioma primary in the right auricle of the heart, with metastases to lungs, bronchial lymph nodes, mesentery, vertebrae, and skull, describe the concomitant finding of benign cavernous hemangiomata in the liver and esophagus. Since benign cavernous hemangiomata are usually multiple and widespread, the authors ponder the possibility that such a benign tumor might have been present originally in the heart wall and later undergone malignant change. Ogilvie and Mackenzie (8) press the premise that, as a group, tumors arising from vascular endothelium can be shown to run in a series of increasing malignancy, beginning with the congenital vascular nevus, proceeding to simple angioma, then to malignant angioma, finally ending in malignant hemangioendothelioma. Sweitzer and Winer quote Fraser as having postulated that hemangioendothelioma occurs as the result of the further evolution of a hemangioma which, after its formation, continues to grow by infiltration and active endothelial proliferation. Ewing (4) wrote that, in considering the "etiology of endothelioma, the influence of chronic irritation, trauma, and low-grade infection must be given a prominent place." Caro and Stubenrauch (2) report a case in which a hemangioendothelioma

[1] From the Department of Radiation Therapy, Dr. Ira I. Kaplan, Director, Bellevue Hospital, New York, N. Y. Accepted for publication in December 1946.
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TABLE I. RESULTS OF TREATMENT OF HEMANGIOENDOTHELIOMA

Procedure	Stout's Series			Sweitzer and Winer's Series			Author's Series		
	Number of Times Performed	Number of Recurrences	Died with Metastases	Number of Times Performed	Number of Recurrences	Died with Metastases	Number of Times Performed	Number of Recurrences	Died with Metastases
Surgery	21	12	6	8	6	0	2	0	1
Irradiation	0	0	0	1	1	0	0	0	0
Surgery + Irradiation	0	0	0	3	0	0	2	0	0

developed at the site of an injury, with wide invasion and a fatal outcome four months after the patient was first seen. Three of Sweitzer and Winer's patients gave a history of trauma; yet these writers declare that trauma cannot be considered as transforming a previously benign angioma into hemangioendothelioma.

PATHOLOGY

The term "hemangioendothelioma" was first used by Mallory in 1908, to describe a malignant vascular tumor in which the endothelial cell is responsible for the aggressive growth and metastatic properties of the lesion. It has been described as a tumor made up of frequently anastomosing vascular tubes lined by atypical, hyperchromatic endothelial cells of varying size and shape which may form one layer or several layers, or may proliferate to such a degree as to obliterate completely the vascular tubes. The endothelial cells are generally within these tubes, but at times are found growing outside their confines in solid sheets. A delicate framework of reticulin fibers supports the vascular channels. The blood does not circulate through the tumor because of the immaturity of most of the vessels, although in the center there may be found some mature capillaries and larger vessels.

For malignant vascular tumors, as is true of so many other groups of tumors, there is, unfortunately, no generally accepted classification or terminology. Ewing listed hemangioendothelioma as "hemangioma hypertrophicum cutis" and defined it as "a slowly growing tumor of the skin or subcutaneous tissue occurring chiefly in children, in which there is a nearly diffuse growth of endothelial cells with imperfect formation of capillaries." Geschickter (5) does not favor the term hemangioendothelioma, and the nearest thing to it in his classification is called a "metastasizing hemangioma," which is defined as "a superficial cellular angioma of the angioblastic variety which has been present as a benign growth for many years and which shows marked activity following trauma, and then metastasizes widely." Stout completely doubts the existence of "benign metastasizing hemangiomas." He studied the published reports of several such cases and, on re-examining the pathological specimens of the primary growths, found atypical endothelial cells as well as numerous anastomosing vascular tubes which convinced him that the tumors were hemangioendothelioma to begin with, and not simple benign hemangiomas.

CLINICAL FEATURES

Hemangioendothelioma may occur at any age, but more than half of the cases reported were in persons less than thirty years old. There is apparently no marked sex preponderance; of the cases collected by Stout, Sweitzer and Winer, and the writer, 15 were in males and 13 in females. The tumor varies in size from 0.5 cm. to 15 cm. or more in diameter (Fig. 1) and shows no predilection for any special part of the body, having been reported in the skin and subcutaneous tissues (2, 6, 10, 11), the breast (10), bones (3), tonsils, lungs, pleura, mediastinum, heart (7), pericardium, liver (8), spleen, lip, stomach, intes-

tine, retroperitoneal space, ovary, uterus, corpora cavernosa, orbit, and central nervous system. The growth is not tender or painful. The cutaneous tumor is usually raised well above the surface, and the enveloping skin is normal until it is injured by trauma, at which time it will break down and there will be considerable bleeding, either outwardly from the surface of the tumor or inwardly into itself. Usually the tumor is soft and red. The rate of growth varies but is most often slow and progressive.

Metastases, which are common, occur through the blood stream, and sometimes through the lymphatics. Sites of metastatic involvement are the lungs, liver, spleen, pancreas, kidneys, adrenals, bones, skin, lymph nodes, diaphragm, and peritoneum. A feature of the tumor which has not been sufficiently stressed is a tendency to local recurrence after surgical removal. One of Stout's cases recurred eight times in nineteen years, and in one of Sweitzer and Winer's cases there were four recurrences in nine years.

The course of the disease varies. It can be a fulminating one, as in a case described by Stout in which the patient died eight weeks after first noticing the tumor in her breast; or it can be protracted, as in another case described by Stout, in which the patient had a tumor on the eyelid for twenty years.

Hemangioendothelioma cannot be definitely diagnosed clinically, since marked vascularity and hemorrhagic tendencies are not sufficient criteria for classifying a neoplasm as a malignant tumor of vascular elements. Histologic study is necessary.

Hemangioendothelioma has to be differentiated from hematoma, hemangioma, granuloma pyogenicum, malignant endothelioma, and Kaposi's disease (idiopathic multiple hemorrhagic sarcoma). A hematoma is present shortly after trauma, is usually tender, and histologically shows only blood clot. A hemangioma occurs in infancy or childhood, is generally flat, and histologically will show single layers of normal endothelial cells lining mature vessels and dilated blood-filled capillaries. It must be remembered that hemangiomas are due to some impairment of the venous drainage mechanism in the involved area, resulting in stasis, engorgement, and dilatation of the vessels within the lesion, but without any inclination to malignant change. A malignant endothelioma shows a great predominance of cellular elements with little tendency to the formation of vessels. Granuloma pyogenicum shows no local infiltration, has a superficial purulent crust, and presents the usual polymorphonuclear response to inflammation. Kaposi's disease is characterized by bluish-red infiltrations which usually involve the lower extremities and, histologically, by blood vessel increase and dilatation, small hemorrhages with deposits of hemosiderin, and changes indicative of fibrosarcoma.

TREATMENT

According to Sweitzer and Winer, wide, thorough excision is enough to effect a cure of hemangioendothelioma but recurrence is possible. The recurrent tumor, fortunately, is as amenable to treatment as the original growth. The lesion is also responsive to irradiation, and Baumann-Schenker goes so far as to say that its radiosensitivity sometimes approaches that of the lymphoblastomata. Another method of treatment is a combination of surgery and immediate postoperative irradiation. Radiation therapy may be administered with x-rays or with radium. The choice will be determined by the accessibility of the lesion, its extent, and the type of modality available. Whether one uses superficial or high-voltage x-ray therapy will depend upon the thickness of the lesion and its location in the body.

A table showing the methods of treatment and results in the cases reported by Stout, Sweitzer and Winer, and the writer, is presented. Stout's series of 18 cases included 12 that had only surgical excision of the tumor, with local recurrences in 5, including the case previously mentioned with nine recurrences in twenty years.

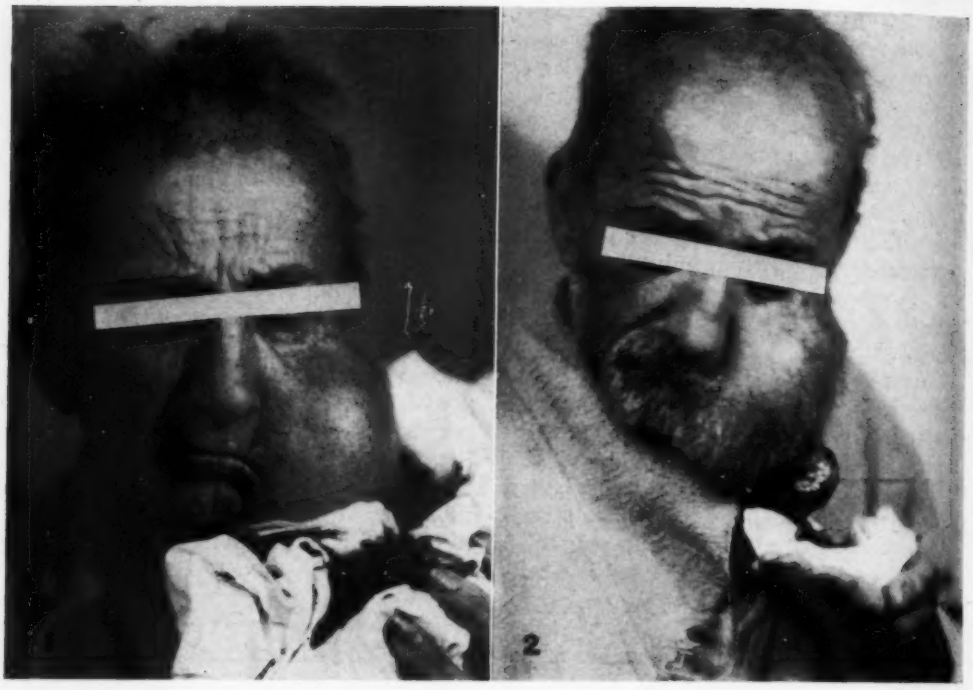

Fig. 1. Illustrating the large size that a hemangioendothelioma can attain. Note that the dependent portion of the tumor has broken down and is oozing blood.

Fig. 2. Demonstrating the smaller, bleeding outgrowth from the dependent, posterolateral region of the large hemangioendothelioma of the cheek.

Sweitzer and Winer's series of 6 cases included 4 treated by surgery only, with local recurrences in 3 (4 recurrences in a nine-year period in one). Irradiation combined with surgery in 3 instances resulted in no recurrences as late as twelve years after treatment though, oddly enough, 2 of the 3 patients had shown recurrences after previous treatment by surgery alone. In the writer's group of 4 cases, 2 had surgery only and the remaining 2 had irradiation after surgical excision. Of the former, 1 died with metastases and 1 was not traceable; the latter were alive one and a half and seven years, respectively, after treatment. Combining these figures, it is found that among 31 cases treated only by surgery, there were 18 local recurrences, while in 5 cases in which surgery was followed by irradiation there were no local recurrences.

REPORT OF CASE

A. K., a white male aged 56, was admitted to Bellevue Hospital on March 5, 1945, in a semi-stuporous condition. He gave a confused story of having been struck on the head by another man and complained of a severe headache. His family history and past history were vague but apparently non-contributory.

There was a round, non-tender, fluctuant mass in the patient's left cheek, as large as a baseball (3 inches in diameter). The overlying skin was not ecchymotic and there was no break in the buccal mucosa subjacent to the mass. Other findings were ecchymosis of both eyelids bilaterally, edema of the scalp, blood in the right nostril, bilateral spasticity, ankle clonus, and a positive Babinski reflex. Pulse, temperature, blood pressure, blood count, Wassermann reaction, and spinal tap were normal, but x-rays revealed a vertical fracture through the right frontal bone, terminating in the inner region of the right orbit and extending backwards into the parietal bone. The left mandible showed no evidence of fracture. A diagnosis of fracture of the skull and hematoma of the left cheek was made.

On March 7, 1945, the mass in the left cheek was incised and about an ounce of "currant-jelly" clot

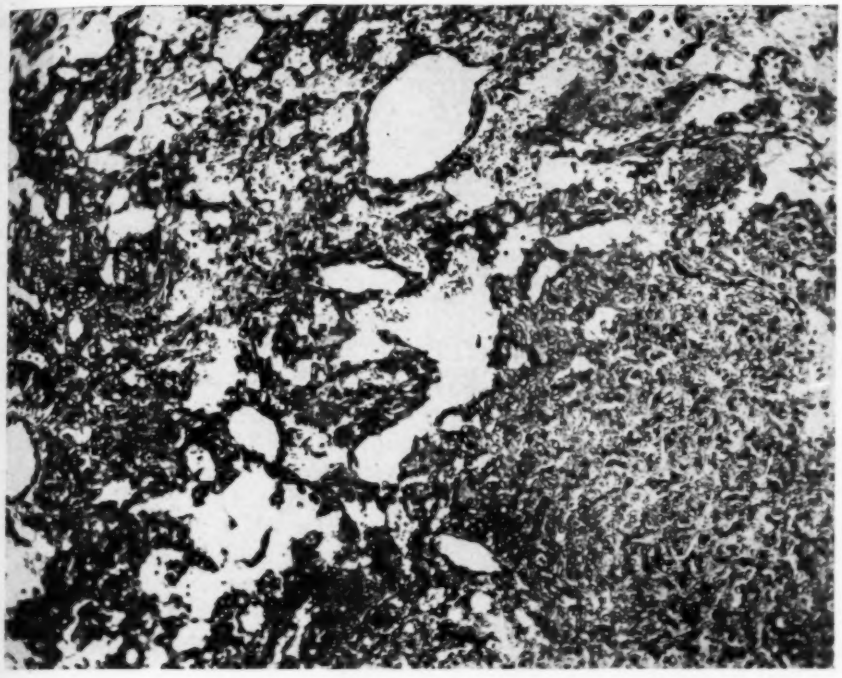

Fig. 3. Photomicrograph of hemangioendothelioma, showing malignant endothelial cells massed in solid sheets, in lower right field. Throughout the remainder of the field, these cells are seen arranging themselves to form vascular channels. (× *c.* 130).

was evacuated. There was profuse bleeding, and a pressure dressing was applied. On March 13, a mass as large as the original one had re-formed at the operative site, and two days later it was again incised. More thin "currant jelly" clot was expressed, and the ensuing hemorrhage was again checked by packing and pressure bandage. In neither instance was the blood clot sent to the laboratory for study. The patient was discharged on March 29, 1945.

On Nov. 27, 1945, he was re-admitted to the hospital because the mass in his cheek had recurred. It was now much larger than it had been on his previous admission and had been bleeding almost continually for the past three weeks. He stated that about four months after his discharge from the hospital, the tumor had begun to grow again. Two months later, a smaller growth arose from the lower portion of the large tumor and soon began to ooze blood.

Examination disclosed a large round mass, measuring 6 inches in diameter and elevated about 2 inches above the left cheek surface (Fig. 1). The overlying skin was normal in color, tense, fluctuant, and non-tender. Springing from the posterolateral, dependent portion of the tumor was a smaller, spherical mass, about 1 1/2 inches in diameter, which had an ulcerated, granulating skin surface that bled repeatedly (Fig. 2). At this time, the patient appeared weak and chronically ill. Heart and lungs were normal; there was no hepatic or splenic enlargement, and no enlargement of the cervical, axillary, or inguinal lymph nodes. The blood count showed hemoglobin 7.5 gm.; red blood cells 2,240,000; white blood cells 9,200 (72 per cent polymorphonuclear leukocytes, 26 per cent lymphocytes, and 2 per cent monocytes). Urinalysis was normal, and x-ray examination of the left facial bones showed no evidence of fracture. A biopsy specimen from the smaller mass, taken on Dec. 6, 1945, was reported as an angiomatous tumor, but tissue from the deeper portions of the mass was requested for a better study.

On Dec. 11, 1945, under intratracheal anesthesia, the external carotid artery was ligated, and the tumor was completely excised. It had to be resected from the parotid and submaxillary glands and the muscles of the cheek, down to the mucous membrane of the buccal cavity. In resecting it from the parotid gland, the nerve structures entering the gland, which included the facial, were divided. Five days later, left facial paralysis was evident, and ten days after the operation an external salivary fistula developed, which, however, closed spontaneously.

The histologic report on the surgical specimen described the tumor as composed mainly of broad

Fig. 4. Appearance of patient after surgical removal of the mass. Note the extent of the scar and the classical signs of facial paralysis due to severance of the facial nerve.

sheets of cells with large, pale, oval to round nuclei, and a moderate amount of light-staining, eosinophilic cytoplasm. In several areas, these cells, typical of malignant endothelial cells, were seen to be forming moderate-sized vascular channels, some of which contained red blood cells. A few mitotic figures were present. With Wilder stain the endothelial cells of the newly formed vascular tubes were shown to be enclosed by a fine framework of reticulin fibers. The diagnosis was hemangioendothelioma (Fig. 3).

The patient was referred for postoperative radiation therapy on Jan. 10, 1946. At this time, further questioning brought out the startling fact that about a year before his first admission to the hospital he had noticed a small reddish "sore" in the midportion of his left cheek. The "sore" progressed slowly at first but then began to grow more rapidly; just before he came into the hospital, it was about as large as a baseball, as stated above. The tumor did not bleed, was not painful, and did not interfere with eating. There had not been any trauma to the face prior to the appearance of the "sore."

Examination in the Radiation Therapy Clinic disclosed a long, vertical, healed scar on the left cheek, extending from near the external canthus of the eye, down over the mandible to the upper portion of the neck (Fig. 4). The skin of the cheek in the region of the scar was hard and non-tender, the firmness extending through the cheek thickness. There was no swelling of the face, but a typical left facial paralysis was present.

Deep x-ray therapy was administered directly over the scar: 200 r (air dose) three times weekly, through an 8 × 10-cm. portal, carried to a total of 2,000 r. The technical factors were: 200 kv., 20 ma., 50 cm. skin-target distance, 0.5 mm. Cu and 1.0 mm. Al filtration, h.v.l. 0.9 mm. Cu.

When the patient was discharged from the clinic on Feb. 4, there was a mild epidermitis of the cheek, no epithelitis, and no evidence of local recurrence On re-examination in the clinic, on July 16, 1947[2], the skin showed no signs of radiation reaction and there was still no evidence of recurrence.

COMMENT ON CASE

Several interesting questions present themselves for consideration when this case is reviewed. To begin with, was the tumefaction of the cheek a hemangioendothelioma when the patient was first admitted to the hospital on March 5, 1945? Might this have been determined if the "clots" which were then expressed from the mass had been studied microscopically? If so, should not all extravascular blood clots removed from subcutaneous and deep tissues be studied histologically for possible evidence of vascular neoplasia?

Could the tumor in the cheek originally have been a hemangioma and have undergone a transformation into hemangioendothelioma as a result of the head trauma? Hemangiomas, however, are usually congenital, and manifest themselves long before the age of fifty-five, when this patient first noticed his lesion. There was x-ray evidence of a fracture on the *right* side of the skull with bleeding from the *right* nostril, but the tumor was on the *left* side of his head. The argument can be offered that there might have been a *contre coup* fracture—that the blow had been applied to the left side of the head and the force transmitted to the right side, but there was no ecchymosis and no other evidence of injury on the left cheek. It is highly improbable that this patient had had a hemangioma transformed by trauma into a hemangioendothelioma. The evidence does not favor such an inference.

[2] After this report was in the printer's hands.

CONCLUSIONS

Most hemangioendotheliomata first come to the attention of the surgeon, and the method of attack is usually entirely at his discretion. Partly because most of these tumors are so readily accessible, and partly because they are not considered as highly malignant, simple surgical excision only is performed.

The summary in Table I shows that the best results are to be expected from surgical treatment in conjunction with radiation therapy. It is our firm belief that combined surgical and radiological treatment of hemangioendothelioma offers the hope of better control, and a more frequent cure, of a tumor which occasionally behaves like a benign growth but which more often takes on the character of a highly malignant process terminating in widespread metastases.

SUMMARY

(1) Hemangioendothelioma is a rare, slowly growing malignant tumor. Only 8 cases were seen and treated at Bellevue Hospital in twenty-two years.

(2) It is our opinion that the best treatment for this tumor is surgical excision followed by irradiation.

(3) An unusual case is reported.

NOTE: My thanks are tendered to Dr. Rieva Rosh, Radiation Therapist at Bellevue Hospital, for her aid in the preparation of this paper, and to Dr. W. C. Von Glahn, Director of the Department of Pathology, for his help in the collection and presentation of the pathological data.

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SUMARIO

Hemangioendotelioma

En la mayor parte de los casos los hemangioendoteliomas son primeramente observados por el cirujano a cuya discreción suele quedar por completo el método de tratamiento. En parte porque en la mayoría de esos tumores el acceso es fácil y en parte porque no se les considera muy malignos, el procedimiento habitual consiste en la simple excisión quirúrgica. El análisis de tres series de casos tomadas de la literatura revela, sin embargo, que se obtienen mejores resultados cuando la cirugía va seguida de la irradiación bien con los rayos X o el radio. Entre 31 casos tratados exclusivamente con la cirugía, hubo 18 recurrencias locales y 7 muertes debidas a metástasis. Entre 5 casos que recibieron irradiación postoperatoria, no hubo recurrencias. Parece, por lo tanto, que la cirugía combinada con la radioterapia es el tratamiento de elección del hemangioendotelioma, ofreciendo un pronóstico más favorable en una forma de tumor que se comporta a veces como un tumor benigno, pero que más a menudo reviste la naturaleza de un proceso sumamente maligna, culminando en metástasis generalizadas. El caso descrito en este trabajo corrobora esta conclusión.

Influence of Dose Fractionation on the Lethal X-Ray Effect Produced by Total Body Irradiation in Mice

A Preliminary Note[1]

FRIEDRICH ELLINGER, M.D.[2]

In previous investigations it has been demonstrated that in various animal species increasing doses of x-rays in the form of total body irradiation produce an increasing mortality rate (1, 2). Data concerning the influence of dose fractionation on the lethal effect produced in mice by total body irradiation are presented in this paper.

The influence of dose fractionation on the biologic effect of x-rays has been the subject of a large number of investigations. From the accumulated evidence it appears that fractionation usually decreases the effect of a given dose administered in one exposure. In certain tissues and organs with high reproductive capacity, however, as, for example, the testis (3) and malignant tumor tissue (4), the effect of the fractionated dose was found to be more pronounced.

The mammalian body is composed of tissues known to react differently to dose fractionation. A study of its influence on the organism as a whole appears, therefore, of special interest.

METHODS

A total of 253 white male mice has been used in these experiments. The radiation factors employed were as follows: 200 kv.p., 10 ma, 0.25 mm. Cu and 1.0 mm. Al inherent filtration, corresponding to a half-value layer of 0.75 mm. Cu. The intensity of the radiation was 23.4 r/min. The distance from the target to the animal container was 50 cm., and the total field size 20 × 20 cm. The set-up for the exposures was the same as in our previous experiments (2).

Doses of 1,000, 500, and 400 r/air were given in one exposure and in fractions of 100 r/air on consecutive days (simple dose fractionation). These single exposure doses according to our previous experiences represent the LD 100, 50, and 35, respectively.

The choice of 100 r/air as the dose for each fraction of treatment was determined by previous experience, which showed that this dose represents the maximum effective dose, *i.e.*, the dose which in single exposure produces a marked effect within the irradiated body without causing fatalities.

Mortality rates for both groups, those receiving the radiation in a single exposure and those receiving the same total dose in equal installments, have been established by recording the number of fatalities daily. A graphic presentation of the results is made, as previously, by using the days after exposure as abscissa values and the percentage mortality as ordinate values. For correct comparison the graphs for the fractionated treated animals have been transformed in such a manner that the zero day in the fractionated group is the day on which the total dose in this group has been accomplished (*e.g.*, zero day for 500 r fractionated is the fourth day after beginning of treatment).

RESULTS

As shown in Figure 1, fractionation of each of the three investigated doses results in a decrease in the mortality rate.

The significance of these observations is illustrated in Figure 2. In this graph the lethal effect of the single exposure is presented in such a way that the total number

[1] From the Laboratory for Experimental Radiation Therapy, Long Island College of Medicine, Brooklyn, N. Y. Accepted for publication in December 1946. This work was aided by grants from the John and Mary R. Markle Foundation and William R. Warner & Co., New York.

[2] Research Associate in Radiology, Long Island College of Medicine.

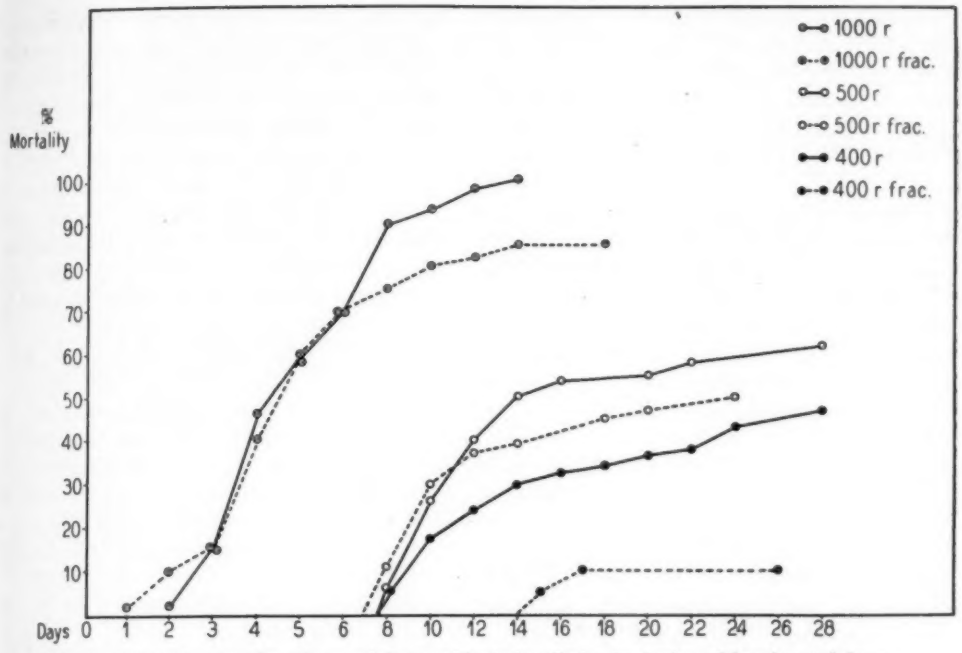

Fig. 1. Mortality rates for mice receiving total body irradiation in single and fractionated doses.

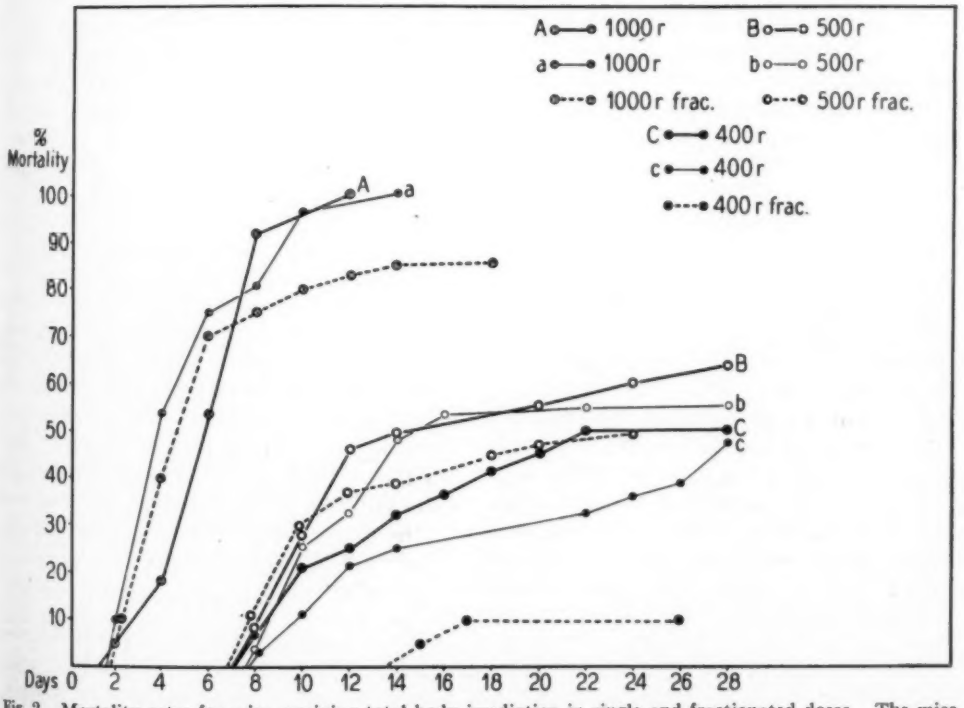

Fig. 2. Mortality rates for mice receiving total body irradiation in single and fractionated doses. The mice receiving single doses are in each instance divided into two subgroups. See text.

of mice used for each dose has been divided into two groups and the mortality rate plotted for each subgroup (*A* and *a*; *B* and *b*; *C* and *c*). These two subgroups, permit appraisal of the consistency of the lethal effect for each of the three doses given in single exposure. As shown in Figure 2, in each instance the lethal effect of single exposure doses proved higher than that of the same dose fractionated.

The decrease in mortality rate in the mice receiving fractionated doses was accompanied by less pronounced changes in the general appearance of the animals. The fur appeared less ragged, and the loss in body weight in those animals which received 500 r was also less pronounced.

Autopsies of mice dying following fractionated treatment showed the same changes in the spleen and bone marrow and fatty changes in the livers previously described in those dying from the same doses given in a single exposure (2, 5).

DISCUSSION

It has been demonstrated that the lethal effect of certain x-ray doses given to mice as total body irradiation is decreased by simple fractionation. This phenomenon is most pronounced with the dose which produces the lowest mortality rate in a single exposure, as was to be expected.

Our data appear of particular interest in view of the recent studies by Henshaw (6) concerning the influence of fractionated irradiation on the life span of mice. Henshaw's interest was mainly focused on the determination of the tolerance dose in x-ray protection. His experimental approach, therefore, differed fundamentally from ours. He irradiated mice with minute daily doses of x-ray over the entire lifetime. The doses used ranged from 5 to 25 r/air, which doses in his experience, when given once, did not influence the white blood count. The exposures took place five times weekly. Even with the smallest dose of 5 r/air, amounting to as little as 1/200 of the absolute lethal dose (ALD) for mice, a definite shortening of the life span of the irradiated mice was found. This indicates a definite dose accumulation under these very extreme conditions of fractionated treatment. These findings are of great importance in the problem of x-ray protection.

The interest of the radiation therapist in the problem of dose fractionation in total body irradiation is different. His clinical problem is whether or not a cancericidal dose of x-rays can be applied to the body as a whole without severe damage to the tumor host.

The demonstration that simple fractionation of lethal doses of x-rays decreases the mortality rate appears, therefore, of great significance. The fact that such a decrease has been accomplished by using single fractions amounting to as much as the maximal dose which can be given in a single exposure without producing fatalities seems particulary encouraging, as these doses are definitely effective on tumor tissue.

The data presented should be considered only as a qualitative result. They certainly do not permit any conclusions as to the amount by which fractionation decreases the effect in total body irradiation. They do, however, indicate the possibility of developing fractionated treatment schemata which will be far less dangerous to the host without impairment of the cancericidal action. The importance in the experimental radiation therapy of malignant tumors appears evident.

The proved consistency of the lethal effect of x-rays in mice is another interesting result of these investigations. This consistency is remarkable in view of the fact that these experiments have been conducted over a period of two years. Our data thus demonstrate the suitability of the lethal effect produced by total body irradiation of mice for quantitative studies of radiation effects.

SUMMARY

A comparison has been made between the mortality rates produced by various doses of x-rays given as total body irradiation to mice (*a*) in one exposure and (*b*)

in equal fractions on consecutive days (simple dose fractionation). It has been demonstrated that simple dose fractionation decreases the mortality rates caused by the same doses when given in one exposure. This decrease in mortality rate was found to be most pronounced with the dose which produced the lowest mortality rate in single exposure.

ACKNOWLEDGMENT: The author wishes to express his gratitude to Dr. A. L. L. Bell, Director of the Department of Radiology, Long Island College of Medicine, for his interest in and support of these investigations.

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SUMARIO

La Fraccionación y el Efecto Letal de los Rayos X

Comparados los coeficientes de mortalidad producidos por varias dosis de rayos X (1,000 r, 500 r y 400 r, en el aire) administradas a ratones en forma de irradiación total del cuerpo (*a*) en una exposición, y (*b*) fracciones iguales de 100 r en el aire en días consecutivos (fraccionación simple de dosis), quedó demostrado que la fraccionación simple rebaja la mortalidad ocasionada por las mismas dosis administradas en una sesión. Esta disminución de la mortalidad resultó ser más pronunciada con la dosis que produjo la mortalidad más baja en una sola sesión.

EDITORIAL

Roentgen Therapy of Carcinoma of the Esophagus

That the radiation therapy of carcinoma of the esophagus presents us with one of our most difficult problems is universally recognized, more especially as no other form of treatment can claim equally good results from the standpoint of mortality or morbidity. The relative radioresistance of squamous-cell carcinoma and the usual extent of the growth before the occurrence of symptoms create a difficult primary problem, which is further complicated by the rather rapid involvement of the neighboring lymph nodes and the proximity of vital structures. To these difficulties are added the irritative effects of foods and fluids constantly passing over the involved area and eventual obstruction, leading to deterioration of the general health and inability to tolerate radical forms of therapy.

In assessing the results obtained from various types of therapy, consideration must be accorded the site of the tumor. Carcinomas involving the cervical portion of the esophagus are much more amenable to radiation therapy, since an adequate dose of radiation is more easily applied here, and the results are statistically better than for other esophageal cancers. In the thoracic portion, the esophagus is not only at a greater distance from the skin, making it more difficult to apply an adequate tumor dose, but it also lies in close proximity to vital organs whose presence gives the radiologist justifiable concern. Tumors in the region of the cardia are also relatively inaccessible, and their irradiation may involve considerable exposure of the liver, spleen, and stomach, resulting in leukopenia and other constitutional effects.

Radium therapy, extensively employed in the past for esophageal carcinoma, has been largely discontinued because of its ineffectiveness and the untoward accidents which have attended it. The use of the radium bougie has given the best results, and a number of cases are recorded in the literature with survivals for varying numbers of years without evidence of recurrence of the original lesion. The disadvantages of the method are the local trauma, with imminent danger of perforation of the esophagus, and the high local dosage with rapid decrease of the depth dose, thus affording insufficient irradiation of adjacent lymph nodes.

Published series of carcinomas of the thoracic portion of the esophagus indicate that roentgen therapy is the most effective method of palliation, overcoming the obstruction with the least discomfort and danger to the patient. Uniform irradiation of the tumor and surrounding area is possible, and the danger of local trauma is eliminated. Even in this area the number of permanent cures is low. Excessive dosage may be delivered to the surrounding structures, as the lungs and the heart, and the tumor dose is therefore necessarily limited.

A careful study of 51 cases of carcinoma of the esophagus has been reported by Smithers, Clarkson, and Strong (3). Of the 51 cases referred for roentgen therapy, 44 were accepted and in 32 treatment was completed. In 5 of the 32 cases, the bulk of the tumor was in the upper third of the esophagus, in 21 in the middle third, and in 6 in the lower third. The radiation was given through six fields, 20 × 4 cm., at 400 kv., 80 cm. focus-skin distance, with a half-value layer of 3.7 mm. Cu. Six of the patients were living at the time of the report. One was alive and well four years after treatment, the others at various intervals, from thirteen to thirty-two

months. Eight of the patients who died lived a year or more after treatment and one more than two years. In 3 who died of metastases, all local symptoms had disappeared. In no case was there evidence of fibrosis of the lungs, nor was there evidence of cardiac damage in any instance. The skin effect was negligible, with only a mild erythema in most cases.

In a small series of 5 cases, Buschke and Cantril (1) employed 800 kv., 100 cm. target-skin distance, and 4.5 mm. lead filtration. One patient with involvement of the distal portion of the esophagus and the lesser curvature of the stomach was alive without radiological evidence of local recurrence after three and one-half years. These authors believe that approximately 5,000 r must be delivered to the tumor and state that this is possible through one anterior and one posterior field.

A series of 36 cases of cancer of the thoracic esophagus treated with medium-voltage roentgen therapy has been reported by Strandqvist (4). The factors used were 170–180 kv., target-skin distance 50 cm., filter 0.5 mm. Cu plus 1.0 mm. Al. Strandqvist attempted to attain a tumor dose of 5,000 r over a period of forty days, but this goal was not always reached, even though six skin portals were used. The skin and lung reactions were somewhat more annoying than in cases treated by others with higher voltage. Injury to the heart due to direct irradiation of the cardiac region was observed in several cases. This was a late complication and was not observed until six months to a year after treatment. In this series of 36 cases there were 4 patients who lived two years or longer. Of these, 2 were living and well at the time of the report. Eighteen patients died within one year. The author concludes that one cannot attain lasting cure without producing excessive damage to vital intrathoracic organs.

From the Radium Center in Copenhagen, Nielsen (2) reports preliminary results of treatment of 174 cases of carcinoma of the esophagus by rotation therapy, at 180 kv. with 0.5 mm. Cu filtration. The great majority of these—166, or 95 per cent—were situated entirely within the thoracic esophagus. The patient is seated on a rotating stool and the position of the roentgen tube is fixed. Fluoroscopy is used for centering the beam on the lesion and the rotation time is ten to fifteen minutes. A tumor dose of about 5,000 r was given over a period of five to eight weeks. The skin reaction was mild, consisting of a moderate dry epidermitis. The general reaction was also slight, but there was usually a drop in the systolic blood pressure. No final results are as yet available, but in 117 cases complete or nearly complete freedom from symptoms was obtained. Contrasting the results with his previous results with cross-fire irradiation, Nielsen shows that 25 per cent of the patients as against 10 per cent in the former series were alive after one year. Corresponding figures for two years were 15 and 4 per cent.

It would seem from this brief review of the treatment of cancer of the esophagus that the results are much improved when voltages of 400 kv. or more are employed for standard cross-fire irradiation. A possible exception is the series treated by Nielsen with rotation therapy, though he believes that even better results would be obtained with supervoltage rays. It is also noted that damage to the skin and even to the lungs and heart were less at the higher voltages. The results appear to indicate that with supervoltage irradiation of carcinoma of the esophagus we may hope for a moderate number of cures, while relief will be obtained in a high percentage of cases.

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ALABAMA RADIOLOGICAL SOCIETY

At a recent meeting of the Alabama Radiological Society, the following officers were elected: President, Dr. John Day Peake of Mobile; Vice-President, Dr. Lewis E. Sorrell of Birmingham; Secretary-Treasurer, Dr. Courtney S. Stickley of Montgomery. Dr. Karl Kesmodel of Birmingham was nominated as candidate for Councilor to the American College of Radiology.

RADIOLOGICAL SOCIETY OF NEW JERSEY

At a recent meeting of the Radiological Society of New Jersey, the following officers were elected: President, Dr. H. R. Brindle, of Asbury Park; Vice-President, Dr. Wm. H. Seward, of Orange; Secretary, Dr. Raphael Pomeranz, of Newark; Treasurer, Dr. C. A. Plume, of Succasunna; Counselor, Dr. Francis Carrigan, of Newark.

NORTH CAROLINA RADIOLOGICAL SOCIETY

At a meeting of the North Carolina Radiological Society at Virginia Beach, on May 13, Dr. C. E. Howard of Goldsboro was elected President for the ensuing year; Dr. J. P. Rousseau of Winston-Salem, Vice-President; Dr. James E. Hemphill, Charlotte, Secretary-Treasurer.

The meeting followed that of the Radiological Section of the North Carolina Medical Society, under the chairmanship of Dr. G. W. Murphy, of Ashville, in which the following speakers participated: Dr. Stuart Gibbs, Bowman Gray School of Medicine, Dr. Robert J. Reeves, Professor of Radiology, Duke University School of Medicine; Dr. Robert H Hackler, Washington, N. C.; Dr. James E. Hemphill, Charlotte; Dr. C. L. Gray, High Point; Dr. Allan Tuggle and Dr. Thomas A. Murrah, Charlotte Memorial Hospital.

TENNESSEE RADIOLOGICAL SOCIETY

The Tennessee Radiological Society at its recent annual meeting elected the following officers for the coming year. Dr. J. Cash King of Memphis, President; Dr. Franklin B. Bogart of Chattanooga, Vice-President; Dr. J. Marsh Frère of Chattanooga, Secretary-Treasurer.

Dr. U. V. Portmann of Cleveland, Ohio, addressed the Society on "Roentgen Therapy for Some Superficial Lesions." Dr. Portmann was also guest speaker on the Tennessee State Medical Society program, his subject being "The Role of Surgery and Radiation Therapy for Cancer of the Breast."

DR. WARREN W. FUREY HONORED

At its Annual Dinner on June 18, Dr. Warren Furey took office as President of the Chicago Medical Society. Members of the Radiological Society of North America, recognizing Dr. Furey's invaluable services on their own behalf, congratulate their medical colleagues of Chicago on the wisdom of this choice.

NATIONAL CANCER INSTITUTE

The resignation of Dr. R. R. Spencer as Chief of the National Cancer Institute of the U. S. Public Health Service to be effective July 1 was announced at the last quarterly meeting of the Institute's National Advisory Council, in Bethesda. Dr. Spencer will, however, continue his valuable work in the field of cancer, devoting his full time to professional education and research. His successor as head of the Institute is Dr. Leonard A. Scheele, formerly Assistant Chief. Dr. A. C. Ivy, Vice-President of the University of Illinois and one of the country's leading physiologists, becomes Executive Director of the National Cancer Advisory Council, succeeding Dr. George M. Smith, who resigned some months ago for reasons of health.

In Memoriam

EBEN J. CAREY, M.D.

1889–1947

Eben J Carey, Dean and Professor of Anatomy in Marquette University School of Medicine, died of acute infectious hepatitis in Columbia Hospital, Milwaukee, on June 5, 1947, after a short illness. While he was primarily an anatomist, Dr. Carey was keenly interested in radiology and had been a member of the Radiological Society of North America since 1929.

Eben J Carey was born in Chicago, July 31, 1889, and acquired his preliminary education in California. He then went to Creighton University, Omaha, where he received the degrees of Master of Science and Doctor of Science and taught in the Department of Anatomy. In 1920 he went to Marquette University as Professor of Anatomy. Continuing his medical studies at Rush Medical School, he received his M.D. from that institution in 1925. In 1934 he became Dean of the School of Medicine at Marquette.

Dr. Carey was nationally known as an anatomist, and many honors came to him. His skill in the preparation of scientific exhibits was well recognized: he served as Director of Medical Exhibits at the Cen-

EBEN J. CAREY, M.D.
1889–1947

tury of Progress Exposition and from 1931 was Director of Medical Exhibits at the Museum of Science and Industry in Chicago.

For his work on the x-ray study of bone growth, Dr. Carey was awarded the Gold Medal of the Radiological Society of North America in 1933. He was most sympathetic to the teaching of radiology to undergraduate students, and during his last school year he rearranged the teaching schedule so that time was available for the Department of Radiology to teach first-year students roentgen anatomy and to double the time given the junior class.

Eben Carey was a man of strong convictions and worked hard for the cause of organized medicine. He was a friendly man and a jovial companion. His presence at a meeting insured keen discussion and good fellowship.

Radiology has lost a strong proponent in his passing but medicine is richer because of his efforts.

S. A. MORTON, M.D.

DR. ALBAN KÖHLER

Word has been received of the death of Dr. Alban Köhler of Wiesbaden, Germany. Dr. Köhler was an Honorary Fellow of the American College of Radiology and was well known to American radiologists for his book on "Borderlands of the Normal and Early Pathological in the Roentgenogram," a work which has gone through many German and English editions. A letter from Dr. Köhler, telling of the losses which he suffered in the war, appeared in RADIOLOGY for November 1946.

Book Reviews

ENGLISH-SPANISH CHEMICAL AND MEDICAL DICTIONARY, COMPRISING TERMS EMPLOYED IN MEDICINE, SURGERY, DENTISTRY, VETERINARY, BIOCHEMISTRY, BIOLOGY, PHARMACY, ALLIED SCIENCES AND RELATED SCIENTIFIC EQUIPMENT. By MORRIS GOLDBERG, Chief Technical Translator, Translation & Research Bureau, New York City. Author of *Spanish-English Idioms*. A volume of 692 pages. Published by McGraw-Hill Book Company, Inc., New York 18, N. Y. Price $10.00.

An English-Spanish Chemical and Medical Dictionary should find a wide field of usefulness among chemists, physicians, laboratory workers, and others who are searching for Spanish equivalents to scientific terms in active English usage. According to the publishers more than 40,000 translations and definitions are included in this new dictionary by Morris Goldberg. Radiologists, however, will find that many words which are commonplace in their specialty are missing. Perhaps the most serious omission is the term *roentgen*, indicating the international unit of radiation dosage. Others, to select a few, are tomography, laminagraphy, grenz rays, cyclotron, betatron, isotope, phantom, diaphragm (Bucky), neutron, and proton.

The author makes a point of the fact that not only are Spanish equivalents of the English terms presented but that there are included, in addition, brief definitions in Spanish for correct and ready interpretation. This is an excellent idea, but in a work designed to cover so wide a field it has been impossible to extend these definitions beyond a few words, so that the general impression is one of oversimplification. It is assumed, however, that the book is designed for rapid reference rather than an intensive word study, in which case one should perhaps not be too critical

The typography is excellent, and the general appearance of the book pleasing. It should constitute one more link in the bond of understanding between scientists of the Americas.

RADIOLOGICAL SOCIETIES: SECRETARIES AND MEETING DATES

Editor's Note: Secretaries of state and local radiological societies are requested to cooperate in keeping this section up-to-date by notifying the editor promptly of changes in officers and meeting dates. Address: Howard P. Doub, M.D., The Henry Ford Hospital, Detroit 2, Mich.

UNITED STATES

RADIOLOGICAL SOCIETY OF NORTH AMERICA. *Secretary-Treasurer*, Donald S. Childs, M.D., 607 Medical Arts Bldg., Syracuse 2, N. Y.

AMERICAN RADIUM SOCIETY. *Secretary*, Hugh F. Hare, M.D., 605 Commonwealth Ave., Boston 15, Mass.

AMERICAN ROENTGEN RAY SOCIETY. *Secretary*, Harold Dabney Kerr, M.D., Iowa City, Iowa.

AMERICAN COLLEGE OF RADIOLOGY. *Secretary*, Mac F. Cahal, 20 N. Wacker Dr., Chicago 6, Ill.

SECTION ON RADIOLOGY, A. M. A. *Secretary*, U. V. Portmann, M.D., Cleveland Clinic, Cleveland 6, Ohio.

Alabama

ALABAMA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Courtney S. Stickley, M.D., Bell Bldg., Montgomery. Next meeting at the time and place of the Alabama State Medical Association meeting.

Arkansas

ARKANSAS RADIOLOGICAL SOCIETY. *Secretary*, Fred Hames, M.D., Pine Bluff. Meets every three months and annually at meeting of State Medical Society.

California

CALIFORNIA MEDICAL ASSOCIATION, SECTION ON RADIOLOGY. *Secretary*, D. R. MacColl, M.D., 2007 Wilshire Blvd., Los Angeles 5.

LOS ANGELES COUNTY MEDICAL ASSOCIATION, RADIOLOGICAL SECTION. *Secretary*, Moris Horwitz, M.D., 2009 Wilshire Blvd., Los Angeles 5. Meets second Wednesday of each month at County Society Bldg.

PACIFIC ROENTGEN SOCIETY. *Secretary*, L. Henry Garland, M.D., 450 Sutter St., San Francisco 8. Meets annually with State Medical Association.

SAN DIEGO ROENTGEN SOCIETY. *Secretary*, R. F. Niehaus, M.D., 1831 Fourth Ave., San Diego. Meets first Wednesday of each month.

X-RAY STUDY CLUB OF SAN FRANCISCO. *Secretary*, Ivan J. Miller, M.D., 2000 Van Ness Ave. Meets monthly on the third Thursday at 7:45 P.M., January to June at Lane Hall, Stanford University Hospital, and July to December at Toland Hall, University of California Hospital.

Colorado

DENVER RADIOLOGICAL CLUB. *Secretary*, Washington C. Huyler, M.D., Mercy Hospital, 1619 Milwaukee, Denver 6. Meets third Friday of each month, at the Colorado School of Medicine and Hospitals.

Connecticut

CONNECTICUT STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Robert M. Lowman, M.D., Grace-New Haven Hospital, Grace Unit, New Haven. Meetings bimonthly, second Thursday.

Florida

FLORIDA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Maxey Dell, Jr., M.D., 333 West Main St., S. Gainesville.

Georgia

GEORGIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Robert Drane, M.D., De Renne Apartments, Savannah. Meets in November and at the annual meeting of State Medical Association.

Illinois

CHICAGO ROENTGEN SOCIETY. *Secretary*, T. J. Wachowski, M.D., 310 Ellis Ave., Wheaton. Meets at the Palmer House, second Thursday of October, November, January, February, March, and April, at 8:00 P.M.

ILLINOIS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, William DeHollander, M.D., St. Johns' Hospital Springfield. Meetings quarterly as announced

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON RADIOLOGY. *Secretary*, Frank S. Hussey, M.D., 250 East Superior St., Chicago 11.

Indiana

INDIANA ROENTGEN SOCIETY. *Secretary-Treasurer*, J. A. Campbell, M.D., Indiana University Hospitals, Indianapolis 7. Annual meeting in May.

Iowa

IOWA X-RAY CLUB. *Secretary*, Arthur W. Erskine, M.D., 326 Higley Building, Cedar Rapids. Meets during annual session of State Medical Society.

Kentucky

KENTUCKY RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Sydney E. Johnson, M.D., 101 W. Chestnut St., Louisville.

LOUISVILLE RADIOLOGICAL SOCIETY, *Secretary-Treasurer*, Everett L. Pirkey, Louisville General Hospital, Louisville 2. Meets second Friday of each month at Louisville General Hospital.

Louisiana

LOUISIANA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Johnson R. Anderson, M.D., No. Louisiana Sanitarium, Shreveport. Meets with State Medical Society.

ORLEANS PARISH RADIOLOGICAL SOCIETY. *Secretary*, Joseph V. Schlosser, M.D., Charity Hospital of Louisiana, New Orleans 13. Meets first Tuesday of each month.

SHREVEPORT RADIOLOGICAL CLUB. *Secretary*, Oscar O. Jones, M.D., 2622 Greenwood Road. Meets monthly September to May, third Wednesday, 7:30 P.M.

Maryland

BALTIMORE CITY MEDICAL SOCIETY, RADIOLOGICAL SECTION. *Secretary*, Harry A. Miller, 2452 Eutaw Place, Baltimore.

Michigan

DETROIT X-RAY AND RADIUM SOCIETY. *Secretary-Treasurer*, E. R. Witwer, M.D., Harper Hospital, Detroit 1. Meetings first Thursday of each month from October to May, at Wayne County Medical Society club rooms.

MICHIGAN ASSOCIATION OF ROENTGENOLOGISTS. *Secretary-Treasurer*, R. B. MacDuff, M.D., 220 Genesee Bank Building, Flint 3.

Minnesota

MINNESOTA RADIOLOGICAL SOCIETY. *Secretary*, C. N. Borman, M.D, 802 Medical Arts Bldg., Minneapolis 2. Regular meetings in the Spring and Fall.

Missouri

RADIOLOGICAL SOCIETY OF GREATER KANSAS CITY. *Secretary*, John W. Walker, M.D., 306 E. 12th St., Kansas City, Mo. Meetings last Friday of each month.

ST. LOUIS SOCIETY OF RADIOLOGISTS. *Secretary*, Edwin C. Ernst, M.D., 100 Beaumont Medical Bldg. Meets on fourth Wednesday of each month, October to May.

Nebraska

NEBRASKA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, O. A. Neely, M.D., 924 Sharp Building, Lincoln. Meetings third Wednesday of each month at 6 P.M. in either Omaha or Lincoln.

New England

NEW ENGLAND ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, George Levene M.D., Massachusetts Memorial Hospitals, Boston, Mass. Meets monthly on third Friday at Boston Medical Library.

New Hampshire

NEW HAMPSHIRE ROENTGEN SOCIETY. *Secretary-Treasurer*, Albert C. Johnston, M.D., Elliot Community Hospital, Keene. Meetings quarterly in Concord.

New Jersey

RADIOLOGICAL SOCIETY OF NEW JERSEY. *Secretary*, Raphael Pomeranz, M.D., 31 Lincoln Park, Newark 2. Meetings at Atlantic City at time of State Medical Society and midwinter in Newark as called.

New York

ASSOCIATED RADIOLOGISTS OF NEW YORK, INC. *Secretary*, William J. Francis, M.D., East Rockaway, L. I.

BROOKLYN ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, Abraham H. Levy, M.D., 1354 Carroll St., Bklyn. 13. Meets fourth Tuesday of every month, October to April.

BUFFALO RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Mario C. Gian, M.D., 610 Niagara St., Buffalo 1. Meetings second Monday evening each month, October to May, inclusive.

CENTRAL NEW YORK ROENTGEN SOCIETY. *Secretary-Treasurer*, Dwight V. Needham, M.D., 608 E. Genesee St., Syracuse 10. Meetings in January, May, and October.

LONG ISLAND RADIOLOGICAL SOCIETY. *Secretary*, Marcus Wiener, M.D., 1430 48th St., Brooklyn 19. Meetings fourth Thursday evening each month at Kings County Medical Bldg.

NEW YORK ROENTGEN SOCIETY. *Secretary*, Wm. Snow, M.D., 941 Park Ave., New York, 28.

ROCHESTER ROENTGEN-RAY SOCIETY. *Secretary*, Murray P. George, M.D., 260 Crittenden Blvd., Rochester 7. Meets at Strong Memorial Hospital, third Monday, September through May.

North Carolina

RADIOLOGICAL SOCIETY OF NORTH CAROLINA. *Secretary-Treasurer*, James E. Hemphill, M.D., Professional Bldg., Charlotte 2. Meets in May and October.

North Dakota

NORTH DAKOTA RADIOLOGICAL SOCIETY. *Secretary*, Charles Heilman, M.D., 1338 Second St., N., Fargo.

Ohio

OHIO RADIOLOGICAL SOCIETY. *Secretary*, Henry Snow, M.D., 1061 Reibold Bldg., Dayton 2. Next meeting at annual meeting of the Ohio State Medical Association.

CENTRAL OHIO RADIOLOGICAL SOCIETY. *Secretary*, Hugh A. Baldwin, M.D., 347 E. State St., Columbus.

CLEVELAND RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, George L. Sackett, M.D., 10515 Carnegie Ave., Cleveland 6. Meetings at 6:30 P.M. on fourth Monday, October to April, inclusive.

CINCINNATI RADIOLOGICAL SOCIETY. *Secretary*, Eugene L. Saenger, M.D., 735 Doctors Bldg., Cincinnati 2. Meets last Monday of the month, September to May.

Oklahoma

OKLAHOMA STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Peter M. Russo, M.D., 230 Osler Building, Oklahoma City. Meetings three times a year.

Pennsylvania

PENNSYLVANIA RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, James M. Converse, M.D., 416 Pine St., Williamsport 8. Meets annually.

PHILADELPHIA ROENTGEN RAY SOCIETY. *Secretary*, Calvin L. Stewart, M.D., Jefferson Hospital, Philadelphia 7. Meets first Thursday of each month at 8:00 P.M., from October to May in Thomson Hall, College of Physicians, 21 S. 22d St.

PITTSBURGH ROENTGEN SOCIETY. *Secretary-Treasurer*, Lester M. J. Freedman, M.D., 415 Highland Bldg., Pittsburgh 6. Meets second Wednesday of each month at 6:30 P.M., October to May, inclusive.

Rocky Mountain States

ROCKY MOUNTAIN RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, A. M. Popma, M.D., 220 N. First St., Boise, Idaho.

South Carolina

SOUTH CAROLINA X-RAY SOCIETY. *Secretary-Treasurer*, Robert B. Taft, M.D., 103 Rutledge Ave., Charleston 16.

Tennessee

MEMPHIS ROENTGEN CLUB. Meetings second Tuesday of each month at University Center.

TENNESSEE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, J. Marsh Frére, M.D., 707 Walnut St., Chattanooga. Meets annually with State Medical Society in April.

Texas

DALLAS-FORT WORTH ROENTGEN STUDY CLUB. *Secretary*, X. R. Hyde, M.D., Medical Arts Bldg., Fort Worth 2. Meetings on third Monday of each month, in Dallas in the odd months and in Fort Worth in the even months.

TEXAS RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, R. P. O'Bannon, M.D., 650 Fifth Ave., Fort Worth 4.

Utah

UTAH STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, M. Lowry Allen, M.D., Judge Bldg., Salt Lake City 1. Meets third Wednesday, January, March, May, September, November.

UNIVERSITY OF UTAH RADIOLOGICAL CONFERENCE. *Secretary*, Henry H. Lerner, M.D. Meets first and third Thursdays, September to June, inclusive, at Salt Lake County General Hospital.

Virginia

VIRGINIA RADIOLOGICAL SOCIETY. *Secretary*, E. Latan Flanagan, M.D., 215 Medical Arts Bldg., Richmond 19.

Washington

WASHINGTON STATE RADIOLOGICAL SOCIETY. *Secretary-Treasurer*, Frederic E. Templeton, M.D., 324 Cobb Bldg., Seattle 1. Meetings fourth Monday, October through May, at College Club, Seattle.

Wisconsin

MILWAUKEE ROENTGEN RAY SOCIETY. *Secretary-Treasurer*, C. A. H. Fortier, M.D., 231 W. Wisconsin Ave., Milwaukee 3. Meets monthly on second Monday at the University Club.

RADIOLOGICAL SECTION OF THE WISCONSIN STATE MEDICAL SOCIETY. *Secretary*, S. R. Beatty, M.D., 185 Hazel St., Oshkosh. Two-day meeting in May and one day at annual meeting of State Medical Society in September.

UNIVERSITY OF WISCONSIN RADIOLOGICAL CONFERENCE. Meets first and third Thursdays 4 to 5 P.M., September to May, inclusive, Room 301, Service Memorial Institute, 426 N. Charter St., Madison 6.

CANADA

CANADIAN ASSOCIATION OF RADIOLOGISTS. *Honorary Secretary-Treasurer*, E. M. Crawford, M.D., 2100 Marlowe Ave., Montreal 28, Quebec. Meetings in January and June.

LA SOCIÉTÉ CANADIENNE-FRANCAISE D'ELECTROLOGIE ET DE RADIOLOGIE MÉDICALES. *General Secretary*, Origéne Dufresne, M.D., Institut du Radium, Montreal. Meets on third Saturday of each month.

CUBA

SOCIEDAD DE RADIOLOGÍA Y FISIOTERAPIA DE CUBA. Offices in Hospital Mercedes, Havana. Meets monthly.

MEXICO

SOCIEDAD MEXICANA DE RADIOLOGÍA Y FISIOTERAPIA. *General Secretary*, Dr. Dionisio Pérez Cosío, Marsella 11, México, D. F. Meetings first Monday of each month.

ABSTRACTS OF CURRENT LITERATURE

ROENTGEN DIAGNOSIS

The Head and Neck

The Chest

The Digestive System

The Spleen

The Musculoskeletal System

The Genito-Urinary System

THE HEAD AND NECK

Porencephaly. Eugene P. Pendergrass and Charles R. Perryman. Am. J. Roentgenol. **56:** 441–463, October 1946.

The most widely accepted definition of porencephaly is that of LeCount and Semerak, who describe "a defect communicating with the ventricles or separated from them by a thin layer of brain tissue, and covered on the outside by the arachnoid" (Arch. Neurol. & Psychiat. **14:** 365, 1925). This condition must be considered in the differential diagnosis of masses or contracting lesions involving the brain and, since it is benign, its recognition is important in determining prognosis and therapy.

Porencephaly is broadly classified as developmental or acquired. Congenital vascular defects may cause porencephaly, while the significant acquired factors may be traumatic, vascular, or inflammatory.

Conventional roentgenograms may be negative, but more often some degree of asymmetry is evident. The most common finding is a change in the thickness of the skull on one side. It should be kept in mind that porencephaly is a manifestation of atrophy and may be the underlying lesion in hemiatrophy or underdevelopment. In such a case, the cranial vault on the affected side may be smaller, and there may be thickening or compensatory hypertrophy of the bones, elevation of the petrous ridge, and increased pneumatization of the petrous pyramid, mastoid, frontal and ethmoid sinuses. However, *encephalography or ventriculography is necessary to establish the diagnosis.*

In the 29 cases reviewed by the authors the condition is classified as "lobe," "interlobe," or "hemisphere" porencephaly, according to the anatomical location and size of the lesion. Two-thirds of the group had evidence of cortical or subcortical atrophy, such as enlarged lateral ventricles or increase in the size of the subarachnoid pathways. A slight shift of the ventricles is usually present (88 per cent), more often toward the porencephalic side because of the accompanying atrophy. Reports are included of 3 cases which clinically and roentgenographically could not be distinguished from mass lesions.

ELLWOOD W. GODFREY, M.D.

War Injuries to the Mastoid and the Facial Nerve. David Myers. Arch. Otolaryng. **44:** 392–405, October 1946.

Injury to the mastoid area and facial nerve is rare. Of a total of 4,400 battle casualties requiring surgical treatment at one military hospital, only 12 were of this type.

Within the temporal bone are many vital structures in a small area, so that the entrance of a foreign body may produce much damage. Often there are fractures of the dural plate or the lateral sinus plate and/or injury to the dura or lateral sinus. Blood, devitalized tissue, damaged bone, and foreign bodies present ideal conditions for bacterial growth, and the combination of infection and injuries to important structures may lead to dangerous intracranial or systemic infection. Clinically few symptoms may be present to indicate the amount of damage, and the real extent of the injury is learned only at the operating table. There was purulent drainage from the middle ear and the mastoid area in all the patients in this series.

Roentgen studies are invaluable in injuries of the mastoid region. The examination requires detailed exposures of the area in at least two projections. It may be expected to reveal accurately the presence and location of foreign bodies, fractures, and, in most cases, infection. Fractures tend to be more extensive and inflammatory changes more advanced than is apparent in the roentgenogram. Occasionally inflammatory changes are present in the mastoid cells when there is no x-ray evidence of infiltration.

The author believes that too much reliance is placed on chemotherapeutic agents, and that chemotherapy cannot take the place of surgical intervention nor compensate for incomplete surgical treatment in cases of the type under consideration. When an injury is localized to the mastoid, a complete mastoidectomy should be done. If the middle ear is involved as well, then a tympanomastoidectomy is indicated. A foreign body in the mastoid area also calls for mastoidectomy, which makes it possible to ascertain the extent of the injury and remove both the foreign body and injured bone structures. This will result in rapid recovery. Otherwise a long period of disability may be anticipated, with continued suppuration and the ever-present threat of a dangerous complication. Injuries of the facial nerves present a special problem of diagnosis and treatment.

The 12 cases are presented in detail and a number of roentgenograms are reproduced.

THE CHEST

The Dynamic Concept of Thoracic Topography. A Critical Review of Present Day Teaching of Visceral Anatomy. Ernest Lachman. Am. J. Roentgenol. **56:** 419–440, October 1946.

The author enlarges and expounds the concept that the surface relationships of the thoracic viscera as determined in the cadaver differ in many respects from those in the living and cannot, therefore, serve as a proper norm for clinical purposes. The contents of the subdivisions of the mediastinum in the erect subject do not coincide completely with those found in the supine cadaver. According to anatomical teaching the bifurcation of the trachea is at the level of the intervertebral disk between the fourth and fifth thoracic vertebrae or at the level of the upper border of the fifth thoracic vertebra, corresponding to the sternal angle between the manubrium and the body of the sternum. Roentgenography, however, reveals that in the upright adult subject it is usually considerably lower. It is highest in infancy and participates in the general descent of the viscera which takes place during the life span of the individual.

Many factors contribute to make the configuration of the heart extremely variable in the living; foremost among these is the position of the diaphragm, which is influenced by respiration, body posture, the state of filling of the abdominal viscera, fat contents of the abdomen, etc. Other factors are the constitutional type of the individual, the age and sex, weight and

height, and the cardiac phase and pulse rate. The posterior inferior boundaries of lungs and pleura in the living are likewise not in complete agreement with conventional anatomical teaching. According to the latter, the lungs and pleural cavities are separated posteriorly by a wide mediastinal space in which the esophagus is located directly in front of the spinal column. In contrast to this, roentgenograms occasionally depict the presence of a prevertebral space which is occupied by lung and pleura. The inferior pulmonary and pleural boundaries as shown roentgenographically are at a lower level than in anatomical preparations, and the pleural reflection frequently shows an upward concavity which has been wholly disregarded in textbook descriptions.

Lachman believes that as far as topographical anatomy is concerned, studies on cadavers should be replaced, wherever possible, by roentgenographic investigation in the living, which has already proved its value.

ELLWOOD W. GODFREY, M.D.

Solitary Pulmonary Tumor. Cyst-Like Tumors Associated with Anomalies of Ribs. Edgar Wayburn. Am. Rev. Tuberc. **54:** 413–417, October–November 1946.

The author reports 4 cases of a solitary, sharply circumscribed tumor found in U. S. Air Force personnel during a routine chest survey of 77,480 individuals. In each instance the lesion was small, measuring up to 3.5 cm. in diameter, and was located in the lower posterior right lung. In 3 of the cases there were associated rib anomalies (one patient had a cervical rib and the other two bifid anterior ends of the right fourth rib) which are believed to indicate the congenital nature of the pulmonary lesions. The opinion is expressed that they are bronchial cysts. Surgical exploration did not seem justifiable in view of the lack of symptoms and absence of disturbed function. The diagnosis, therefore, is only presumptive and no follow-up examinations are recorded.

L. W. PAUL, M.D.

Tuberculosis Survey Among Chinese Students. R. Tak Eng. Am. Rev. Tuberc. **54:** 385–388, October–November 1946.

In a survey conducted during 1940 and 1941, before the Japanese occupation, a total of 5,234 students in private schools in Hong Kong were tuberculin tested. Of these, 88.2 per cent showed a positive reaction. Even in the age group from six to ten, 77.9 per cent reacted positively; above the age of 16 the percentage exceeded 90. Of the positive reactors, 4,651 were examined fluoroscopically, and 131 cases of tuberculosis were found (2.8 per cent). An additional 11 cases of pulmonary tuberculosis were found among teachers. Since tuberculous infection seems to be universal among the Chinese population in Hong Kong, the tuberculin test will be eliminated in future work, as only fluoroscopy and radiography are necessary for the detection of clinical tuberculosis.

L. W. PAUL, M.D.

Recurrent Spontaneous Emphysema of the Mediastinum with Concomitant Pneumothorax: Report of a Case. J. D. Schendstok. New England J. Med. **235:** 511–513, Oct. 3, 1946.

Spontaneous pneumothorax is important because of the possibility of injured ribs, coronary disease, or myocardial infarct. It is quite possible that this condition occurs more frequently than is generally recognized.

The author's patient, a 37-year-old white male, complained of a tight feeling in the lower chest, radiating along the left side of the neck. Previous experience of a chest pain had led to hospital admissions on various earlier occasions. The patient himself noticed a rhythmic noise within his chest that sounded like water dropping on a shelf. The noise was easily recognized by a visitor, and a physician heard it at a distance of about 5 or 6 feet. Examination at this time (December 1942) showed a pulse of 80 that was slightly irregular. The respirations, however, were normal, without dyspnea or cyanosis. Percussion of the chest showed an unusual degree of tympany over the cardiac area. Roentgenologic examination of the esophagus in various positions failed to reveal any evidence of an esophageal diverticulum or hernia.

The complaints subsided in a relatively short time, but in May 1943 the patient had another experience of dull pain in the cardiac and left infraclavicular areas, again with audible rhythmic sounds heard at some distance from the chest. Several days later a complete examination showed some tympany over the cardiac region, but the only laboratory finding beyond normal limits was a white blood count of 12,100. About two weeks after the onset of this episode a peculiar knocking sound could be heard with a stethoscope over the chest, apparently synchronous with some of the heart beats although skipping others. X-ray films of the chest at this time failed to reveal any evidence of air in the mediastinum, but in oblique views a very small, marginal left-sided pneumothorax could be seen, which was quickly absorbed.

Discussing mediastinal emphysema, the author states that pain is the predominant feature, although it may be entirely absent. It may radiate to the back, the neck, or to the left arm. Subcutaneous emphysema sometimes accompanies mediastinal emphysema. A frequent and important sign is the tympanic sound over the precardial area on percussion; however, the most characteristic finding is the very audible sound of the heart beat, even without a stethoscope, at a considerable distance from the chest. Roentgenologically air may be demonstrated in the mediastinum, often best in an oblique position. Spontaneous mediastinal emphysema is believed to be due to air escaping from the bronchial tree and following the vascular trunks to the mediastinum, where it collects in large amounts. There is frequently an associated pneumothorax, and when one condition is present a search should be made for the other.

JOHN B. MCANENY, M.D.

THE DIGESTIVE SYSTEM

Diverticula of the Lower Thoracic Esophagus. Report of Six, Four of Which Were Operated Upon. Robert M. Janes. Ann. Surg. **124:** 637–649, October 1946.

Six cases of diverticula of the lower thoracic esophagus are reported. The condition is uncommon but should be considered as a possible cause of difficulty in swallowing and substernal distress. Diagnosis is based on the clinical history and barium studies of the esophagus. In 2 of the 6 cases, however, the condition was suspected from the plain roentgenogram. Preoperative and postoperative films are reproduced.

Diverticula responsible for symptoms, and possibly

all that may be described as giant diverticula, should be operated upon. In spite of the fact that only 1 of the 4 patients operated upon in this series could be considered a good operative risk, there was no death as a result of the procedure. Routine postoperative use of penicillin should decrease the danger of infection.

Pharyngo-Esophageal Diverticulum: Its Management and Complications. Frank H. Lahey. Ann. Surg. **124:** 617–636, October 1946.

As the title implies, this paper deals chiefly with the surgical treatment of pharyngo-esophageal diverticulum. With regard to the roentgen diagnosis, the author states that a roentgenogram of a pulsion esophageal diverticulum is so distinctive that one would hardly think it possible to be mistaken as to its diagnosis, but such is not the case. In patients with a high web in the esophagus, in certain patients x-rayed postoperatively some time after removal of an esophageal diverticulum, and in others with high narrowing of the esophagus, there will be a dilatation with a spherical appearance roentgenologically which may lead the inexperienced observer to assume that what is really only a local dilatation is a true diverticulum. A true diverticulum is distinguished by the demonstration of its body, neck, and the spill-over into the esophagus of the thin barium mixture after the sac is filled. In most cases this spill-over appears in the lateral view as a thin line running from the neck down behind the sac. In those cases in which there is only a dilatation, if this thin line is visible, it emerges from the bottom, most dependent portion of the sac, where the narrowed point is, and in the lateral view will never be seen behind the suspected diverticulum.

Volvulus of the Stomach. Carl A. W. Zimmermann III. South. M. J. **39:** 782–786, October 1946.

The author reports in detail the case of a 71-year-old man presenting repeated vague attacks of "indigestion." The attacks had occurred since childhood and appeared to be associated with fatigue or excitement. Among the complaints were epigastric fullness, pain, a sensation as though "food would not pass," followed by relief after noticeable food progress. Sometimes there was precordial oppression followed by belching.

Fluoroscopic examination showed the position of the stomach to be higher than normal. The rugal pattern was disturbed and peristalsis was not observed, the barium trickling through the pylorus. The course of the duodenum was directly downward. The patient was examined at a later date, apparently during an acute attack. The uppermost portion of the stomach was the corpus, which exhibited an air bubble outlining the greater curvature. The stomach was apparently rotated forward and upward on a horizontal axis.

Postmortem examination performed about ten years after the patient first came under observation showed an adhesion between the gastrocolic ligament and the left leaf of the diaphragm. The greater curvature in the extreme right border of the fundus was tipped anteriorly to a moderate degree.

This is the second case of volvulus of the stomach reported by Dr. Zimmermann. FRANCIS F. HART, M.D.

Duodenal Septum. Otis F. Lamson. West. J. Surg. **54:** 384–389, October 1946.

Duodenal septum is a rare congenital anomaly. Only 24 cases have been recorded and these in most instances were found postmortem. The symptomatology is dependent upon the size and location of the opening in the septum. Even with a small opening, symptoms are not likely to be observed until the child begins to take solid food. The opening may then become obstructed and a fatal termination may ensue. The picture is one of high intestinal obstruction, similar to that due to other causes. Sometimes a flat abdominal film will reveal a gaseous dilatation of the duodenum.

Duodenal septum, like atresia and diverticula, is an embryological defect. Once it is discovered, treatment consists in prompt removal.

The author reports a case in a woman of 28 with a history of "stomach trouble" since the age of two. The septum was discovered when the author performed a duodenojejunostomy for an enormously dilated duodenum. The opening in this case was laterally placed on the superior part of the septum, which probably accounts for the patient's survival. The solid food which would have obstructed a central opening was held back and largely digested in the duodenum, passing through the opening in liquid form.

MAURICE D. SACHS, M.D.

Chronic Ulcerative Colitis in a Girl. Agustin Castellanos and Raúl Pereiras. Bol. Soc. cubana de pediat. **17:** 377–408, October 1945.

A case of chronic ulcerative colitis in a girl of nine and a half years, with typical clinical, rectosigmoidoscopic, and roentgen findings, is presented. The illness began when the patient was three years of age, and therefore at the time of the report was of almost seven years' duration. Four roentgenograms of the colon taken in this period are reproduced. During the last three years the patient has shown a surprising improvement on sulfa medication. Various sulfa preparations (sulfanilamide, sulfathiazole, sulfapyridine, sulfasuxidine, sulfadiazine) have been tried during the periods of spontaneous relapse, but the majority of the time the patient has been on sulfaguanidine, most recently on talil-sulfathiazole. The cultures were at first positive for the Sonne-Duval dysentery bacillus; after two years of treatment, twelve negative cultures were obtained.

The most surprising fact about this case is the necessity for giving sulfa medication daily to maintain normal stools. The effect is more evident with the insoluble preparations, especially with sulfaguanidine. Sulfasuxidine has shown the same antidiarrhetic action. Each time sulfa is suspended for two or three days, the diarrhea returns. The child has shown an extraordinary tolerance to this medication and during three consecutive years has taken around 2,200 grams of sulfa drugs without anemia, leukopenia, or toxic manifestations of any kind.

Submucous Lipoma of the Colon, with Report of Two Cases. F. G. Runyeon. New York State M. J. **46:** 2272–2275, Oct. 15, 1946.

Lipomas of the colon may be either submucous or subserous. The subserous variety rarely produces symptoms. The submucous type may be symptomless or may give rise to symptoms suggesting obstruction, intussusception, or a malignant growth.

In 109 of 121 lipomas of the colon recorded in the literature the location was satisfactorily determined: 46 per cent were in the cecum and ascending colon, 16 per cent in the transverse colon, and 38 per cent in the

descending colon, sigmoid, and rectum. Considering the relative length of these different segments, the lesion is found six times as often in the right colon as in the transverse and four times as often as in the left colon.

The author stresses the importance of repeated x-ray studies. It has been his experience that a second or even a third examination may furnish information not at first demonstrated.

Two cases quite typical of the disease are reported. In one the lipoma was in the transverse colon and in the other in the descending colon. Both were removed by colotomy and local excision of the tumor with suturing of the bowel wall rather than by radical resection of the involved segment. The author believes that at operation the surgeon can usually differentiate these lesions as benign and so avoid resection, which carries a higher mortality. BERNARD S. KALAYJIAN, M.D.

Roentgen Diagnosis of Volvulus of the Sigmoid with Intestinal Obstruction. Max Ritvo and J. Laurence Golden. Am. J. Roentgenol. **56:** 480–488, October 1946.

Volvulus of the sigmoid is particularly likely to occur if the sigmoid is dilated, long, and redundant. The authors mention chronic constipation, shortening of the mesentery, pressure from pelvic masses, and increased peristalsis as factors leading to such a condition. Clinically the patient may present a long antecedent history of abdominal pain and constipation. The acute attack is not infrequently preceded by some dietary indiscretion or the use of a purgative. The onset may be sudden and dramatic, and collapse and shock are not infrequent. Constipation is profound. Diarrhea with blood and mucus may be present. Cecostomy and intubation are of little help, and despite transfusions and infusions the patient's condition usually grows rapidly worse. In the past the mortality has been high—about 40 per cent—due largely to the difficulty of clinical diagnosis.

In the authors' experience, the survey film of the abdomen will generally indicate low intestinal obstruction without definitely determining the site or nature of the obstruction. A barium enema administered under constant roentgenoscopic control is considered safe and provides invaluable data. Small amounts of barium are administered slowly and discontinued upon determination of the site and nature of the lesion. If the volvulus has produced complete obstruction, the barium will fill only the ampulla of the rectum and lower sigmoid. At this point, a rounded or tapered stenosis is noted, which is smooth in outline and sharply defined. When the obstruction is incomplete, small amounts of barium will pass through the narrowed lumen. Spiral linear densities alternating with narrow radiotranslucent bands over an area several centimeters in length delineate the torsion of the colon. This corkscrew arrangement of the mucosa is more satisfactorily shown on spot-films made with pressure, under fluoroscopic control, and is considered pathognomonic of volvulus. Further fluoroscopic examination, spot-films, and routine roentgenograms are made after evacuation of the barium.

Once the diagnosis is established, surgery is indicated. Five cases of intestinal obstruction produced by volvulus of the sigmoid are included.

ELLWOOD W. GODFREY, M.D.

Diagnosis of Liver Abscess by Means of Thorotrast Hepatosplenography. Robert J. Reeves and Karl A. Youngstrom. Texas State J. Med. **42:** 310–314, September 1946.

The authors quote Ochsner's classification of the causative factors in liver abscess as follows: (1) transportation of virulent organisms through the portal vein from areas drained by the portal system (appendix, rectum, and other parts of the bowel); (2) extension from some contiguous disease process, as cholecystitis and cholangitis, gastric and duodenal ulceration, and subphrenic space infection; (3) trauma, including penetrating injuries with introduction of microorganisms from without and subcutaneous injuries producing devitalization of liver tissue permitting growth of organisms already present in the liver; (4) blood-borne infection with the production of metastatic abscesses; (5) amebic infection, which is the most common cause.

The possibility of peripheral development of abscesses is pointed out, and the accompanying signs are mentioned, such as diaphragmatic bulging and adhesions. [It is not mentioned, however, that in liver abscess there is more apt to be a blunting of the anterior costophrenic angle, whereas in subphrenic abscess arising from without the liver it is the posterior costophrenic angle that is more likely to be blunt.] Centrally located abscesses may be difficult to diagnose, and other lesions enter into consideration, as hepatomas, cholangiomas, cholangiohepatomas of both liver cell and duct elements, and tumors primary in the liver but not of specific hepatic elements (vascular, fibrous, adrenal rests, etc.).

It is in centrally located abscesses without liver enlargement that the use of thorium dioxide is particularly recommended. The senior author reported on this procedure as early as 1933, and in an experience of fourteen years has observed no significant damage from the medium. The average dose for injection is 75 c.c. colloidal thorium dioxide mixed with several hundred cubic centimeters of isotonic solution of sodium chloride. It is injected slowly over a thirty-minute period. The reaction, if any, is mild. In making the injection it is important to avoid infiltration in the subcutaneous tissues, as the thorium is absorbed and produces a hard painful mass. The presence of thorium is noted in the liver in several hours, and a roentgenogram taken a few hours after injection often shows sufficient contrast to outline a cavity or mass. The concentration in the reticuloendothelial cells continues over several weeks, and the liver density increases. Since a liver abscess or tumor is devoid of active reticulo-endothelial cells, it will contain none of the thorium dioxide and will be of lesser density than the surrounding normal tissue. In this manner, the abscess may be easily demonstrated and accurately localized.

Three cases are reported and roentgenograms are reproduced. SYDNEY F. THOMAS, M.D.

Biliary Calculi "Floating Between Two Fluid Levels": Employment of the Upright Position and Compression. Robert Coliez and Richard Hickel. J. de radiol et d'électrol. **27:** 402–409, 1946.

The suggestion for the study recorded here came from several occasions upon which a gallbladder filled with dye was observed with the patient upright. The calculi were seen to float away from the fundus and to

arrange themselves in a horizontal layer, separating the gallbladder shadow into two distinct parts. This observation led to experiments with gallbladders removed at operation, still filled with dye. The authors describe these studies and discuss the physical chemistry involved in stratum formation. The admixture of bile and dye is not a homogeneous one, which accounts for the derivation of two fluid levels.

With regard to the practical aspect of this phenomenon, it is pointed out that compression such as is ordinarily used on the duodenal bulb enables one to visualize floating calculi when they might otherwise escape detection. The compression is applied with the patient upright.

The authors make the additional point that, in trying to establish a differential diagnosis between calculi and papillomata of the gallbladder, the fixation of the latter, demonstrable in this manner, may be of aid.

PERCY J. DELANO, M.D.

Artificial Pneumoperitoneum for the Diagnosis of Subdiaphragmatic Abscess. A. L. Wilkie and J. C. Clark. Canad. M. A. J. **55:** 296, September 1946.

In x-ray pictures made in the upright position after injection into the peritoneal cavity of 750 to 1,000 c.c. of oxygen, absence of a clear space between the liver and diaphragm (or, on the left side, the stomach and diaphragm) is diagnostic of subdiaphragmatic abscess.

THE SPLEEN

Retroperitoneal Splenomegaly. Occurrence in a Case of Leukopenic Plasma Cell Leukemia. Jack W. Bills and O. H. Perry Pepper. Am. J. M. Sc. **212:** 139–142, August 1946.

The spleen, as a result of a rare developmental anomaly, may occupy a wholly retroperitoneal position. Such a condition may produce no symptoms, but may be associated with a left hydronephrosis, perhaps due to the downward displacement of the kidney. The enlarged retroperitoneal spleen, which lies posterior to the stomach and colon, also pushes the left dome of the diaphragm upward. It fails to present to palpation the characteristic splenic edges or notches.

A case is recorded in which the presence of an enlarged retroperitoneal spleen complicated a leukopenic plasma-cell leukemia and added to the difficulty of diagnosis.

BENJAMIN COPLEMAN, M.D.

THE MUSCULOSKELETAL SYSTEM

Paget's Disease: A Statistical Study of Eighty-Two Cases. Frank W. Newman. J. Bone & Joint Surg. **28:** 798–804, October 1946.

In this review of 82 cases of Paget's disease, the incidence was found to be equally distributed between the two sexes. The disease is one of late middle life, with extremes of twenty-one years and seventy years in the series recorded here. No familial tendency was apparent in any of the histories, although there was a history of diabetes in four of the families, but none of gigantism or hyperparathyroidism.

Only about half of the patients had complaints directly referable to the disease. These included pain in the bone or pain in the distribution of the cranial nerves. The remaining cases were discovered during examination for other reasons. The pelvis was most frequently involved, with the skull second, followed by the spine and femur. Chemical studies showed the blood calcium and blood phosphorus levels to be within normal limits. Serum-phosphatase levels varied from 0.1 to 2.0 units; alkaline-phosphatase levels from a low of 2.6 units to 48.8 units.

Roentgenographic examination was considered to offer the most characteristic findings. These were usually described as "coarse trabeculations, osteoblastic lesions, osteolytic lesions, thickening of the cortex, new-bone production, bone destruction, cotton-wool appearance, marked degenerative changes, and areas of increased and decreased density." The possibility of metastatic carcinoma of the prostate had to be considered in many of these cases.

Complications usually encountered with Paget's disease were: (1) cranial-nerve pressure, (2) fractures, (3) urinary calculi, and (4) sarcomatous degeneration. Cranial-nerve pressure occurred in 26.8 per cent of the patients and usually involved the visual or auditory apparatus. Fractures occurred in 18.3 per cent, with union ensuing within a reasonable period of time. Urinary calculi were found in about 5 per cent of patients. Chondrosarcoma was observed twice.

X-ray therapy for Paget's disease has been practically abandoned. The most recent treatment consists in the administration of magnesium carbonate and a diet low in calcium.

JOHN B. MCANENY, M.D.

Secondary Myelofibrosis with Progressive Generalized Osseous Eburnation. S. R. Bersack and H. R. Feinstein. Am. J. Roentgenol. **56:** 470–479, October 1946.

Apart from primary myelofibrosis, fairly widespread fibrosis of bone marrow may occur in Paget's disease, myeloma, neoplastic osteal processes, bone metastases from prostatic carcinoma, septicemia, benzene and radiation poisoning, hyperparathyroidism, the various granulomatoses, and "spent" polycythemia. There are two prerequisite clinical elements: (*a*) destruction of a substantial portion of the blood-forming bone marrow and its replacement by a connective-tissue derivative; (*b*) an attempt at compensatory hyperplasia by the remaining hemopoietic tissue. Such signs as weakness, bone pains, splenomegaly and refractory anemia are directly predicated upon bone marrow replacement and the recruitment of all available resources for the production of blood constituents.

Both primary and secondary myelofibrosis may occur with and without osseous changes. According to Rosenthal and Erf (Arch. Int. Med. **71:** 793, 1943), about 50 per cent of the patients with myelofibrosis show on roentgen examination mottled rarefactions or irregular condensations in the cortical portions of the bones and splintering or elevations of the periosteum. Diffuse osteosclerosis is found in only a small percentage of cases.

The authors report a case of secondary myelofibrosis with progressive generalized osseous eburnation due to skeletal metastases from prostatic carcinoma. Only two similar cases are described in the English literature.

ELLWOOD W. GODFREY, M.D.

Bone Infarcts. Case Report with Autopsy Findings. S. C. Kahlstrom and D. B. Phemister. Am. J. Path. **22:** 947–953, September 1946.

This is an autopsy study of a previously reported case of bone infarction (Am. J. Roentgenol. **47:** 405, 1942.

Abst. in Radiology **40:** 533, 1943) which was diagnosed roentgenologically before death by the presence of blotchy medullary shadows of increased density produced by calcification of the unresolved portion of the infarcts. The authors believe that routine roentgenography of the bones of the extremities preceding autopsy would assist greatly in the recognition of old infarcts. A diligent routine search at postmortem examination would lead to the discovery of lesions in the early stages and help to arrive at the cause in those cases which remain unexplained.

Eosinophilic Granuloma of Bone, with Report of Case. John T. Bakody. J. Iowa M. Soc. **36:** 397–400, September 1946.

A case of eosinophilic granuloma of the skull, diagnosed preoperatively, is presented. Treatment consisted of surgical excision followed by roentgen therapy (600 r). A tantalum prosthesis was fitted into the skull defect at the time of primary operation. The patient, a 17-year-old sailor, subsequently returned to duty.

Labor Service and "Shovel Disease." E. Wetzel. Schweiz. med. Wchnschr. **76:** 990–991, Sept. 28, 1946.

The author reports a case of chip fracture of the spinous process of the first thoracic vertebra following exertion. These fractures, induced by muscle pull, are thought to be a hazard of heavy physical exertion, and occur in the lower cervical or upper thoracic spine, especially in C7 or T1. There is no specific therapy.

LEWIS G. JACOBS, M.D.

Pathological Intervertebral Disk and Its Consequences: Contribution to the Cause and Treatment of Chronic Pain Low in the Back and to the Subject of Herniating Intervertebral Disk. Olan R. Hyndman. Arch. Surg. **53:** 247–297, September 1946.

The author distinguishes two entities, the degenerating intervertebral disk, in which the nucleus pulposus and annulus fibrosus are undergoing disintegration, but in which there is as yet no bulge or herniation to cause compression of nerve roots, and the herniating disk, in which a weakened capsule or annulus permits a bulge into the spinal canal. While these conditions are pathologically continuous, the clinical syndromes produced are somewhat different, even though they may coexist, which is the reason for this distinction. Patients in the first group usually give a history of chronic low back pain of years' duration, constantly localized in the lumbosacral region or the sacroiliac joint. There may be associated reflex pain down the posterior aspect of the thigh, but this does not extend below the knee nor is it localized to the sciatic nerve. The pain occurs in periodic episodes, usually associated with physical strain. The use of a soft mattress, which promotes a flexed posture, is also provocative of pain, and there are usually stiffness and pain low in the back when an attempt is made to straighten up after having maintained a fixed posture. The pain is not exaggerated by coughing or sneezing. Physical examination is apt to be of little contributing value.

The herniated disk usually produces pain referred to the sacrum or lumbosacral joint and the sciatic notch, radiating down the back of the thigh and leg or the lateral aspect of the leg to the calf, ankle, or foot. This sciatic pain is present in the absence of low back pain in about a quarter of the patients. While the pain is commonly unilateral, it may occasionally be bilateral. Remissions are characteristic but attacks are prone to become more frequent. Coughing and sneezing practically always aggravate the pain. Paresthesias are almost invariable. Contrary to observations in the presence of degenerating disks, limbering up aggravates rather than relieves the pain. The straight leg-raising test produces pain on the affected side, circumferential measurement may show atrophy of the muscles, and hypalgesia of the sole of the foot and changes in the reflexes are often present. Occasional cases are seen in which an acute rupture of the nucleus pulposus occurs without antecedent disk degeneration, and these are usually more acute and disabling in character.

Roentgen examination shows no characteristic signs on the plain film. While narrowing or collapse of a disk is suggestive, it is not conclusive. When this is accompanied by hypertrophic changes on the posterior lip of the vertebra, however, herniation is always present, usually of many years' duration. One of the principal values of this type of examination is to exclude tumor or other disease from the picture. It should be kept in mind that hypertrophic change, which often accompanies this condition, may be confused with arthritis, and an attempt to distinguish the conditions clinically is essential.

Pathological changes are discussed at considerable length. In summary, the degenerating disk undergoes sequestration; the nucleus pulposus loses most of its water content and becomes fragmented and stringy. Its mucoid structure is replaced by fibrocartilage to some degree. There is, however, no evidence of inflammation or necrosis. The annulus also degenerates and becomes thin, eventually being unable to retain the sequestrating nucleus. The etiology is not clear. The present consensus that trauma plays the important role is questioned. While maldevelopment is probably important, it fails to explain the nature of the pathological changes.

Operation is recommended when the diagnosis of herniation is made. Myelography is usually unnecessary. The technic of operation and the postoperative care are discussed in detail. When proper attention is paid to the criteria for diagnosis, the results are usually highly satisfactory. However, in advanced cases with marked degenerative change, complete relief of symptoms is seldom obtained.

This treatise is a very superior discussion and will well repay reading in the original.

LEWIS G. JACOBS, M.D.

Value of the X-Ray Examination in the Diagnosis of Ruptured Intervertebral Disc. Harold O. Peterson. Minnesota Med. **29:** 904, September 1946.

The author points out the fact that the diagnosis of posteriorly herniated disk is not an easy one; that the most important feature of the diagnostic procedure is an examination by a clinician skilled in the approach to this entity; that roentgen signs may be misleading in themselves, unsupported by adequate clinical confirmation.

This brief article is eminently sensible and comprehensive—the best the abstractor has ever read on the subject of herniated disk. It bespeaks not only an extensive experience in the handling of these patients, but the faculty of excellent judgment on the part of the

essayist. It is particularly recommended to those who have read and been impressed by the articles which ascribe diagnostic powers to air myelograms, projections of the spine in plain films followed by the measurement of minute intervertebral inequalities, or those who believe that intrathecal injection of opaque substances and speculative laminectomies may be casually undertaken. PERCY J. DELANO, M.D.

Bilateral and Multiple Ruptured Discs as One Cause of Persistent Symptoms Following Operation for a Herniated Disc. Francis A. Echlin, Bertram Selverstone, and Walter E. Scribner. Surg., Gynec. & Obst. **83:** 485–493, October 1946.

The authors believe that, in some cases at least, the recurrence or persistence of symptoms following removal of a herniated lumbar disk is due to the presence of bilateral or multiple herniations unrecognized at the original operation. They report a series of 60 cases in which operation was done for a suspected herniation of a lumbar disk. In 56 of these one or more herniated disks were found; in the remaining 4 both the operative and the myelographic findings were negative in spite of strong clinical evidence of herniation.

On the basis of the clinical observations, each of the 60 patients, with 3 exceptions, was believed to have a solitary unilateral herniated disk. Operation, however, showed 14 instances of bilateral or multiple herniations, 23.3 per cent of the 60 cases (6.6 per cent bilateral; 16.6 per cent multiple). Removal of the bilateral herniated disks required bilateral laminectomy.

Owing to the frequency of multiple herniations, the authors believe that myelographic studies with pantopaque are indicated in all cases prior to surgical intervention, although this procedure may be of little use in extreme lateral protrusions.

The authors add the opinion that the high incidence of multiple herniations in their series may be due to the fact that they were dealing with relatively severe cases. They also emphasize the point that operative relief of multiple disk herniation is not enough. Heavy work is particularly likely to precipitate postoperative symptoms in these cases.

The clinical, myelographic, and operative findings in some individual cases are discussed.

JOSEPH P. TOMSULA, M.D.

Complete Dislocations of the Acromioclavicular Joint. The Nature of the Traumatic Lesion and Effective Methods of Treatment, with an Analysis of Forty-One Cases. Marshall R. Urist. J. Bone & Joint Surg. **28:** 813–837, October 1946.

In this paper we have the largest collection of complete dislocations of the acromioclavicular joints reported by any one individual The writer's impression of the great variation of the relationship of the acromion to the clavicle was confirmed by roentgen examination of 100 shoulders of unselected patients who had no complaint referable to the shoulder region. The study showed great variation in the form of the joint and indicated that there are relatively few acromioclavicular joints that correspond to the classical anatomical description. The findings are listed as follows: (1) The articular surface of the clavicle overrides the articular surface of the acromion. (2) The articular surfaces of the acromion and clavicle are nearly vertical and lie in the same plane. (3) The inferior margin of the articular surface of the clavicle underrides the superior margin of the acromion, (4) The articular surfaces are incongruent, and the clavicle overlies the acromion. (5) The articular surfaces are incongruent, and are not in contact at any point. (6) The articular surfaces are incongruent, and the inferior margin of the clavicle underrides the superior margin of the acromion. These possible anatomical variations from the supposed normal joint structure may determine the success or failure of conservative treatment of acromioclavicular dislocations and the incidence of sequelae.

Much of this article is given over to details of treatment. Two observations of possible diagnostic and prognostic importance were noted in the course of the study, although the limited number of cases does not permit positive statements concerning them at this time: (*a*) An increase in the width of the joint space on the injured side, demonstrated roentgenographically, indicates posterior displacement of the outer end of the clavicle, even when the acromion process and the clavicle are correctly aligned. (*b*) Palpable posterior displacement and abnormal mobility of the outer end of the clavicle, after three weeks of healing, indicate the probable failure of conservative methods and the recurrence of the dislocation.

JOHN B. MCANENY, M.D.

Malignant Giant-Cell Tumor of the Bones of the Pelvis, Gluteal and Prostatic Regions. N. Puente Duany. Rev. med. cubana **56:** 678–688, September 1946.

A case of giant-cell tumor invading the pelvic bones and the gluteal and periprostatic regions in a 43-year-old patient is reported. From a clinical point of view it is outstanding because of the slow evolution (ten years) of the tumor and its invasive character, which resulted in the blocking of the lymphatic drainage and compression of the corresponding iliac vein and its tributaries, not usual in benign lesions. Anatomically it differed from cases of malignant giant-cell tumor previously reported; first, it was diffuse; second, it affected at the same time the bones and soft tissues; and third, it did not metastasize to the lung. Roentgen therapy was given; 9,000 r were necessary to make the tumor disappear but produced a radionecrosis and ulceration.

Epiphyseal Coxa Valga: Report of Two Cases. Alvis D. Finch and William M. Roberts. J. Bone & Joint Surg. **28:** 869–872, October 1946.

The usual residual deformity following slipping of the capital femoral epiphysis is a coxa vara. The possibility of a coxa valga has apparently been overlooked, more or less, since no reports of this condition—at least in English—could be found. This report concerns two young Negro girls, both of whom had slipping of the capital femoral epiphysis with a resulting coxa valga rather than the usually seen vara deformity. Roentgenographic study of the pelves showed the head of the femur to have slipped upward, laterally, and anteriorly in both patients.

The importance of recognizing this condition lies in the fact that reduction by forcible internal rotation is contraindicated, since this probably increases the deformity and may lead to a vascular necrosis of the epiphysis. JOHN B. MCANENY, M.D

Tibia Vara. Louis Lamy and Léon Weissman. J. de radiol et d'électrol. **27:** 409–414, 1946.

The authors describe tibia vara as a special form of genu varum, the essential feature of which is a maldevelopment of the inner portion of the upper tibial epiphysis. The tibia angles inward sharply, but there is no real limitation of motion. Over 40 cases of this abnormality have appeared in the literature in the last twenty years.

In their discussion of the radiologic features of this condition, the authors include a number of illustrations. For those who cannot see these, it seems to the abstractor that the essential pathology can be clarified by comparing the developmental fault in these cases with a similar one seen at the lower end of the radius in a Madelung's deformity. In either case, one side of the epiphysis is much thinner than the other, with a resultant articular tilting.

If one is interested in this entity, he will find the authors' discussion of the pathogenesis well worth while; the literature is reviewed and various current theories as to remote etiologic factors are carefully weighed. Treatment is by osteotomy.

PERCY J. DELANO, M.D.

Para-Articular Ossification of the Soft Parts of the Ankle: Complication of Sprain With or Without Fracture of the Shaft of the Ipsilateral Fibula. Charles J. Sutro. Arch. Surg. **53:** 441–447, October 1946.

The author reports 6 cases of sprained ankle in which protracted episodes of pain and swelling were accompanied by local para-articular ossifications. The patients were from eighteen to thirty-five years of age. They all experienced an unusually long convalescence, varying from four to seven months. In 2 patients a simple fracture of the fibular shaft accompanied by sprain led to a similar syndrome after removal of the immobilizing plaster-of-paris boots. On physical examination, there were diffuse swelling and tenderness, ecchymosis, and limitation of motion. Roentgen study demonstrated the presence of a small, thin, vertical plaque in the region of the inferior transverse or posterior ligaments, just posterior to the lower lip of the tibia. This tended to increase slowly in size and density, but did not become attached to the bone. Treatment by reduction in the activity of the ankle, elastic support, and hydrotherapy produced symptomatic improvement but did not lead to absorption of the calcification. LEWIS G. JACOBS, M.D.

Panner's Metatarsal Disease: A Condition of Aseptic Necrosis Simulating March Fracture. R. E. Van Demark and P. V. McCarthy. J. Bone & Joint Surg. **28:** 842–844, October 1946.

A 25-year-old male was suspected of having a march fracture of the left foot, though x-ray films failed to reveal any change. Two months later a change at the distal end of the third metatarsal suggested periosteal reaction, and march fracture was again suspected. Subsequent examination showed destructive and sclerotic changes, which became more marked after an interval of two months. At that time definite cystic change was seen in the distal end of the third metatarsal. Examination ten months after the original complaint showed definite deformity of the metatarsal head.

Aseptic necrosis of the metatarsal is seen less often in the adult than in children. The possibility of the disease must be considered, however, and it must be differentiated from march fracture when the latter is a clinical possibility. JOHN B. MCANENY, M.D.

Skeletal Lesions of the Foot from the Explosion of an Individual ("Antipersonnel") Mine. Le Génissel and R. Sarrouy. J. de radiol. et d'électrol. **27:** 414–418, 1946.

The "antipersonnel" mine described here is the German *Schumine 42*, consisting of a small plastic box containing some 200 gm. of explosive, planted just below the surface of the ground, with a detonator which becomes effective with a weight of 20 to 25 kilos. The resulting explosion cripples the foot of the person stepping upon the mine, causing damage not approximated by anything seen in civilian life.

Roentgenograms showing typical injuries are reproduced. In general these followed two patterns, depending upon whether the forefoot or the heel touched the detonator. In the anterior injury illustrated here, the metatarsals are extensively shattered and displaced, and the tibia is shattered at its lower end; the injury to the great toe is extensive. The fractures, the authors state, are frequently compound. In one case, the explosion virtually accomplished an amputation of the forefoot. In the posterior type, the force of the explosion is expended principally against the os calcis, with great damage and loss of substance. Curiously enough, the talus is frequently intact, with extensive injuries above and below it. Some of the posterior injuries duplicate essentially a Chopart disarticulation.

The films illustrating this paper merit anyone's inspection. The abstractor has never seen in any type of foot injury anything to equal the shattering and comminution which characterize this *pied de mine*, or "mine foot." PERCY J. DELANO, M.D.

Sprain or Momentary Dislocation of the Talus? R. Robert De Nicola. Occupational Med. **2:** 214–218, September 1946.

A type of dislocation of the ankle which may easily be mistaken for a sprain is described. The unfortunate results from inadequate treatment are emphasized.

The serious fault of mistaking a momentary dislocation of the talus for a simple sprain may be avoided by performance of the "inversion test," graphically described by Watson-Jones in his book on *Fractures and Other Bone and Joint Injuries*. Subluxation of the talus is not a common injury, however, and the test is not recommended as a routine procedure in all injuries of the ankle. The test is indicated (1) when the routine lateral and anteroposterior roentgenograms show no bony injury, but the force of injury is known to have been severe, signs of swelling, ecchymosis and tenderness are "excessive," a history of repeated sprains is obtained, or the symptoms from the initial injury are delayed, and (2) when routine films show some tilting of the talus, evidence of an old fracture of the ankle, evidence of traumatic arthritis, or a bone spur on the astragalus.

Two cases of dislocation of the talus are presented, and roentgenograms are shown for comparison with an inversion roentgenogram taken on a recently fractured ankle.

Calcaneo-Scaphoid Bar. R. K. Magee and R. A. Benson. Canad. M. A. J. **55:** 287, September 1946.

This is a brief note describing an unusual anomaly demonstrated radiologically in a 37-year-old soldier. It consisted in a congenital ossification in mesenchyme which would ordinarily form the lateral part of the short plantar ligament, and was demonstrable in an oblique view as a solid bar of bone uniting the antero-internal angle of the calcaneus with the navicular.

THE GENITO-URINARY SYSTEM

Crossed Renal Ectopia. Haakon Ødegaard. Acta radiol. **27:** 543–551, Aug. 31, 1946.

The author presents the following theory as to the development of crossed renal ectopia. Under normal conditions the ureteral bud, which sprouts from the wolffian duct about the 25th day, has a transitory dorsomedial direction of growth. When this ureteral bud continues to grow until it makes contact with the metanephrogenic tissue of the opposite side, a crossed renal ectopia results.

The crossed ectopic kidney is in most cases hypoplastic. It lies below the other kidney and is often fused with it. The hilus usually is anterior to the kidney. The vascular supply, as a rule, is derived from vessels that supply the normal kidney. The ureter crosses the midline usually at about the 5th lumbar vertebra.

This anomaly is seen almost twice as frequently in men as in women. It must be differentiated from extreme degree of floating kidney, double or accessory kidney, displaced horseshoe kidney, and longitudinal ectopia.

The author presents 5 cases of crossed renal ectopia, of which 4 were in men. In all the ectopic kidney was located distal to the normal kidney, three times on the left and twice on the right side.

PAUL W. ROMAN, M.D.

Spontaneous Rupture of the Kidney. Case Report. D. E. Beard. South. M. J. **39:** 780–782, October 1946.

Beard adds a case of spontaneous rupture of the kidney to the 42 which he found previously recorded in the literature. In the reported cases, predisposing causes were hydronephrosis, pyelonephritis, pyelonephrosis, tuberculosis, abscess, infarct, nephritis, tumor, aneurysm, and renal calculus. Parenchymal rupture is followed by sudden severe pain in the involved side, a rapidly appearing mass due to hemorrhage, and shock of varying degree. Two to three days later jaundice, general toxemia, and sepsis may appear. Symptoms and signs of pelvic tears vary, depending on whether urinary extravasation is intra- or extraperitoneal. In the former event, sudden pain is followed by generalized peritonitis; in the latter a rapidly developing perinephritic abscess occurs. Excretory and retrograde pyelography are of diagnostic aid. Films may show extravasation of contrast media, deviation of the ureter around a hemorrhagic mass, obscuration of renal and psoas shadows, fixation of the kidney, and elevation of the diaphragm. The condition is considered a surgical emergency.

The author's patient was a 29-year-old colored laborer complaining of progressive dysuria and frequency for seven years. Cystoscopy revealed a grossly infected bladder of 30 c.c. capacity. A cystogram showed a small contracted bladder, and excretory urography revealed a normal right upper urinary tract with failure of excretion on the left. Fifteen days after admission, while lying quietly in bed, the patient was seized with a sudden knife-like pain in the left upper quadrant which radiated posteriorly. Muscle rigidity and tenderness were marked. The patient was in mild shock. Within a few hours the temperature rose to 103° F., shock disappeared, and a hard, fixed, tender mass was palpable in the left kidney region. A left retrograde pyelogram showed a hydronephrotic kidney with a dense mass lying between it and the elevated diaphragm. Surgical exploration revealed a markedly enlarged left kidney with an intact but tightly distended true capsule. After 500 c.c. of purulent material was aspirated, a subcapsular nephrectomy was done. A small rupture measuring 1 × 1.5 cm. was found at the superior pole, communicating with the superior calyx. *B proteus* was cultured from the specimens. The patient received streptomycin postoperatively and made a satisfactory recovery.

WILLIS MANGES, M.D.

Roentgen Diagnosis of Diseases of the Neck of the Bladder. Athayde Pereira. Am. J. Roentgenol. **56:** 489–499, October 1946.

Pereira considers urethrocystography necessary and even indispensable in the diagnosis of disease of the bladder neck. The following pathological conditions are discussed: valves of the neck, congenital atrophy of the neck, acquired atrophy of the neck, sclerosis of the neck, hypertonia of the sphincter of the neck, and hypertrophy of the trigonal muscle. The author describes his technic, the position of the patient, and the media used for urethrocystography. A brief discussion of accidents which may occur during urethrocystography, as well as contraindications to the procedure, is appended.

ELLWOOD W. GODFREY, M.D.

THE BLOOD VESSELS

Surgically Removed Foreign Body Embolus in the Pulmonary Artery. Sölve Welin, Carl Axel Hamberger, and Clarence Crafoord. J. Thoracic Surg. **15:** 302–307, October 1946.

A 21-year-old youth was struck in the groin by a flat, sharp piece of steel, which entered the femoral vein. The foreign body was never found in the leg, and over a year later, when the patient was being examined for pneumonia, it was seen in the lung at the left base. The past history was at first disregarded, and the foreign body was thought to be in the bronchus, but it was not demonstrable on bronchoscopy with fluoroscopic control and no bronchi were seen leading directly to it. The old history of injury in the leg was then correlated with the roentgenographic and bronchoscopic findings, and it was reasoned that the steel fragment entered the femoral vein and was carried thence to the heart and out into the pulmonary artery. On exploration of the lung the foreign body was, after some difficulty, located inside one of the pulmonary arteries. A small film was placed in a sterile glove, and by holding this behind the suspected area a roentgenogram was made, locating the foreign body. The vessel was then exposed and opened and the piece of steel removed. It measured 10 × 16 mm. There was no thrombotic occlusion of the vessel either before or after removal of the foreign body, and the patient recovered. This is believed to be the

first case in which a foreign body embolus was diagnosed preoperatively, arteriotomy was done, the foreign body removed, and the vessel closed with a good result.

HAROLD O. PETERSON, M.D.

Mediastinal Phlebography. K. Lindblom. Acta radiol. **27:** 521–525, Aug. 31, 1946.

The purpose of this paper is to call attention to the value of visualizing the mediastinal veins in the study of mediastinal tumors. The patient is placed in the left lateral position with a wool pad compressing the right jugular vein. Injection is made into the upraised right arm after venous stasis is produced in the left arm by a tourniquet. During inspiration 20 c.c. of diodrast are injected through a large needle into the right cubital vein within a period of one to two seconds. As soon as the injection is completed, the exposure is made with horizontal rays. If necessary, the procedure may be repeated with the patient lying on the opposite side.

Two cases showed an aneurysm of the innominate artery bulging into the innominate veins. These were proved at autopsy. Two patients had malignant lymphomas of the anterior mediastinum. In one the tumor blocked the left subclavian, the jugular, the innominate, and the caval veins. In the other, the left subclavian vein was blocked.

Five illustrations demonstrate the technic and show the findings in the cases studied.

S. H. MACHT, M.D.

TECHNIC

The Physicist in the Radiodiagnostic Department. M. H. Jupe and L. A. W. Kemp. Brit. J. Radiol. **19:** 301–313, August 1946.

Jupe makes a plea for greater use of physicists in diagnostic radiology, pointing out that progress may be made in improved meters, testing meters and timers, control of incoming power, dark room procedures, better emulsions, body-section radiography, and stereography.

Kemp reports a preliminary study of some of these problems in one department (at the London Hospital) with interesting results.

Tests of timer accuracy showed that an impulse timer had no error. Seconds timers showed errors of from 0 to 100 per cent. A device is described by means of which several timer tests may be made on one film.

There are many difficulties in determining the quality of a diagnostic beam. Preliminary studies showed that the second half-value-layer is more significant than the first. Tests upon two tubes showed a material difference in both quality and quantity. With modern types of line focus tubes there is a significant difference in both quantity and quality along an axis parallel to that of the tube. The intensity is materially less toward the anode end of the tube and the rays are harder, but the increase in hardness is not sufficient to make up for the decrease in intensity.

SYDNEY J. HAWLEY, M.D.

Measurement and Calculation of Unsharpness Combinations in X-Ray Photography. H. A. Klasens. Philips Research Reports **1:** 241–249, 1945–46.

The unsharpness with which a radiographic image is recorded is governed by three principal factors: (*a*) the unsharpness introduced by the finite size of the target of the roentgen tube (so-called geometrical unsharpness); (*b*) the unsharpness introduced by movement of the structure under examination (movement unsharpness); and (*c*) the unsharpness attributable to the characteristics of the screen with which the radiograph is made (screen unsharpness). Methods whereby geometrical unsharpness and movement unsharpness may be calculated for any particular condition are well known and are reviewed by the author. In the main, calculations derived by these methods coincide with observed impressions rather well for either one of these types of unsharpness alone. When the two types of unsharpness occur together, the observed unsharpness that results appears to be a complex function of the two unsharpness values. The complexity is further increased when screen unsharpness also enters the picture. Until recently, methods of measuring and expressing screen unsharpness have not been satisfactory. The author, however, has developed a simple method in which the correlation between observed and calculated screen unsharpness values is extremely good. This same method has been expanded to permit the derivation of an expression by which the calculation of the total unsharpness which occurs when geometrical, movement and screen unsharpnesses are present may be made. This expression may be written, $u_o = (u_g^3 + u_m^3 + u_s^3)\ 1/3$, where u_o, u_g, u_m, and u_s represent the observed, geometrical, movement, and screen unsharpnesses, respectively. Calculations derived from this formula coincide closely with observed data.

RUSSELL H. MORGAN, M.D.

RADIATION THERAPY

NEOPLASMS

Interstitial Irradiation Therapy in Carcinoma Originating at the Limbus. Report of Two Cases Treated With Radium Element Seeds. E. M. Sykes. Texas State J. Med. **42:** 376–379, October 1946.

Two cases of squamous-cell carcinoma of the limbus are described, with photographs before and after excision and the insertion of radium seeds (1.33 mg.). In the discussion which follows it is pointed out that a small plaque can be used quite satisfactorily, furnishing a slightly larger source of radium, with exposures as long as forty minutes. An ingenious method for fixation of the radium is described by Dr. C. M. Griswold.

SYDNEY F. THOMAS, M.D.

Endolaryngeal Surgery Combined with Radiation in Late Laryngeal Cancer. Millard F. Arbuckle. Ann. Otol., Rhin. & Laryng. **55:** 681–689, September 1946.

This is a further report of the author's method of treating inoperable laryngeal cancer by roentgen irradiation following removal of the thyroid cartilage. An earlier paper by Arbuckle, Stutsman, and Moore (Ann. Otol., Rhin. & Laryng. **53:** 689, 1944), describing the procedure and presenting 18 cases has been abstracted quite fully in RADIOLOGY (**45:** 316, 1945).

Eight additional cases have now been treated. In none of these was the growth confined to the true vocal cord. The cancers were not as late, however, nor as widely distributed as those in the earlier series, and the patients were younger and healthier. There was one

death in the series. One patient was still under treatment at the time of the report, and the remainder were well, without evidence of cancer.

The diagnoses (clinical and microscopic) in the 8 cases were: epidermoid carcinoma (grade not given) in 2; epidermoid carcinoma, grade II, in 1; epidermoid carcinoma, grade III, in 2; carcinoma with metastases to lymph nodes and perichondrium (no grading) in 1; squamous-cell carcinoma, grade I, well differentiated, in 1; squamous-cell carcinoma, grade III, in 1. Prior to 1940 laryngectomy would have been recommended in all of these cases. Though the author states that for the cure of cancer larger doses of radiation are necessary than are commonly used, even to the point of burns of the skin and extreme irritation of the mucosa, excessive amounts were not employed in this group—1,800 to 2,600 r to either side of the neck, which is less than in the Coutard fractionated technic.

Since the longest period that has elapsed in any of the cases treated by this method (including the earlier series) is six years, the author does not attempt to prophesy the future results, either as to permanent cure or late radiation reactions. He has had no operative deaths and none due to irradiation. Total laryngeal stenosis had not occurred. One patient had a high degree of stenosis due to loss of the cricoid cartilage, but his voice was still usable. STEPHEN N. TAGER, M.D.

Comments on a Case of Lymphosarcoma of the Tonsil Which Did Not Respond to Roentgen Therapy. Miguel Guerrero Noyer. Rev. med. cubana **56:** 30–37, January 1945.

A case of tumor of the tonsil and left lateral wall of the pharynx in a 7-year-old boy is presented. The tumor had developed over a six months period. A diagnosis of lymphosarcoma was based not only on the type of lymphoid cells of which the tumor was composed but also on its fibrillary stroma and the widespread presence of macrophages. The tumor failed to respond to roentgen therapy (6,000 r), and the patient died three weeks following operation.

Bronchiogenic Carcinoma. Gustaf E. Lindskog. Ann. Surg. **124:** 667–672, October 1946.

A series of 100 unselected cases of primary bronchiogenic carcinoma is analyzed. In 65 cases the growth was considered hopelessly advanced and inoperable when the patient was first admitted. Thirty-eight of these patients received only symptomatic care. Three patients refused treatment. Twenty-nine received high-voltage roentgen therapy, radon implantation, or both. All of these are dead, the shortest period of survival (after admission) being two months and the longest thirty-three. The average duration of life in this group was 7.4 months, an increase of doubtful significance over the untreated cases. However, in the treated group there was very significant palliation in the form of relief of pain, decrease of dyspnea, improved aeration and bronchial drainage, as well as psychotherapeutic benefit.

Surgical exploration was carried out in 32 cases. No positive tissue diagnosis was available in 20 of these patients despite various diagnostic studies. In 20 of the 32 cases a non-resectable tumor was found. Nine of these patients had no subsequent roentgen irradiation and the average life span was eight months; 11 patients receiving roentgen therapy lived an average of 11.8 months. This difference is not statistically significant.

Twelve patients were submitted to surgical resection (10 pneumonectomy, 2 lobectomy), with a hospital mortality of 25 per cent. Three patients (2 pneumonectomy, 1 lobectomy) had survived 2.5, 4.5, and 5.5 years and were clinically well at the time of the report; all had squamous-cell carcinoma.

One patient, with anaplastic carcinoma in the mediastinum, is living and working three and one-half years after roentgen irradiation. He is the only patient in whom roentgen therapy produced a strikingly lasting effect.

Cancer of the Cervix: Study of the Effect of Interstitial Radon Needles as Compared with Roentgen Therapy Given through Intravaginal Cones. Howard C. Taylor, Jr., and Gray H. Twombly. Am. J. Roentgenol. **56:** 513–522, October 1946.

The authors state that this article is simply a progress report obtained by treating equal and comparable groups of cancer of the cervix by two methods thought at the start to be equally effective.

One group was treated by the "divided dose technic," *i.e.*, twelve treatments of 200 r each to each of six fields, 70 cm. target-skin distance, 200 kv., 0.5 mm. copper filtration. Along with this, intravaginal x-ray therapy was given three times a week. With the 3- or 4-cm. cone, three fields of vaginal irradiation, one directly to the cervix and one to each vaginal vault, were usually possible. Typically, the cervix received four treatments of 500 r each (measured in air) for a total dose of 2,000 r. The parametrial treatments of 750 r each were given through a 3-cm. cone pointed into each vault for a total dose of 3,000 r. Two weeks after completion of all roentgen therapy the patient was admitted to the hospital and a radium applicator was inserted into the cervical canal for a dose of 3,000 mc. hours.

The second group received comparable external irradiation—ten treatments of 200 r each to each of six pelvic fields, at 200 or 250 kv. Two weeks after the last treatment the patients were admitted for radium therapy. Four steel sheath needles containing radon gas in gold tubes 2 cm. in active length were inserted into the periphery of the cervix, two in front and two in back, the needles of each pair being separated by 1 cm. One centimeter lateral to each of the first needles was placed another 3-cm. needle, angled out slightly toward the parametria. Finally four needles of 4-cm. active length were inserted, two into each side, at a distance from each other and the neighboring 3-cm. needles of 1 cm. and directed into the parametria at an angle of about 30 degrees. A radon tandem, containing an amount of radon approximately equal to that in all the needles combined, was then inserted into the cervical canal. The total dose was 6,000 mc. hours, approximately 3,000 from the needles and 3,000 from the tandem. In general the needles totaled 100 mc. in strength with the tandem amounting to another 100 mc.

Of 113 patients treated with vaginal cones, 54, or 47.8 per cent, were alive and free of cancer when last examined. Of the 94 cases treated with parametrial needles, 26, or 27.7 per cent, were alive and free of cancer. In the first group 39, or 34.5 per cent, and in the second group 52, or 53.3 per cent, were dead. In the first group 67 were alive, 9 with cancer and 4 possibly with cancer, or 59.3 per cent; in the second group 37 were alive, 7 with cancer and 4 possibly with cancer, 39.4 per cent.

The authors feel that the results with intravaginal cones were uniformly better in all groups, but particularly so in Stages II and III. In addition to the higher expectancy of life, the group treated by vaginal cones enjoyed the advantage of fewer complications of treatment. These complications are detailed and analyzed.

In conclusion, the authors state that "in our experience the use of interstitial radon needles is relatively ineffective and dangerous as a method of controlling cervical cancer and we have abandoned it in favor of intravaginal and external roentgen therapy combined with intracervical radium."

ELLWOOD W. GODFREY, M.D.

Controversial Factors in the Management of Fundal Carcinoma. Lewis C. Scheffey, William J. Thudium, David M. Farell, and George A. Hahn. Am. J. Obst. & Gynec. **52:** 529–540, October 1946.

The authors state at the outset that they are strong advocates of the advantages of irradiation in conjunction with surgery as a planned procedure in the treatment of fundal carcinoma. They then trace the steps which led them to this conclusion, reviewing their experience with 159 cases seen between 1921 and 1945. The length of the period covered makes possible the presentation of five-year results for four different methods of treatment. One hundred and four patients were available for this record, which is as follows:

	Five-year cures
1. Adequate surgery alone	62.5%
2. Radium therapy alone	45.8%
3. Radium therapy combined with external irradiation	36.6%
4. Adequate surgery with preliminary radium (There are 20 survivors in a more recent group of 21 patients who have been followed from one to four years)	90.0%

About 1930 the authors became impressed with the destructive action of radium upon endometrial carcinoma, as observed in removed uteri, and discouraged with roentgen irradiation because of its apparent ineffectiveness postoperatively and the occurrence, in some cases in which it was used prior to operation, of skin changes necessitating postponement of subsequent surgery. The procedure which eventually came into use and has been employed whenever possible since 1935 calls for 4,500 to 5,000 mg. hrs. of radium (screened with 1.5 mm. of platinum) followed in six to eight weeks by complete hysterectomy with removal of the adnexa.

Whenever it is thought that endometrial cancer is deeply invasive or has passed beyond the confines of the uterus, deep x-ray therapy is used to supplement the radium. The low survival rate in this group of patients, as given above, might be expected because the lesions were relatively far advanced.

It is felt that radium has a distinct advantage when used preoperatively not only because it causes local cancer destruction (residual carcinoma, often attenuated, was found in 54.8 per cent of the removed uteri) but because it may devitalize the growth even at some distance from the radium. RUSSELL WIGH, M.D.

Wilms' Tumor. A Review of Sixteen Cases. Reed M. Nesbit and Frederick M. Adams. J. Pediat. **29:** 295–303, September 1946.

A series of 16 cases of histologically proved Wilms' tumor in children, treated at the University of Michigan Hospital during a nine-year period, is presented. Three of the cases did not entirely conform with the usual pathologic picture but are included in the series because they were indistinguishable clinically from a typical Wilms' tumor. Two of these cases were diagnosed as adenocarcinomas, one of which might have been a variant of a Wilms' tumor; the third was diagnosed as a teratoma.

The diagnosis of a Wilms' tumor is not difficult. In a child, usually under five years of age, with a history of progressive abdominal enlargement and a firm, nontender, smooth or finely nodular mass which usually fills half the abdomen, one can quickly make a presumptive diagnosis. The second most common abdominal tumor in childhood, and the one which gives the most difficulty in differential diagnosis, is the sympathoblastoma, or neuroblastoma, of the adrenal. Diagnosis is usually established by pyelography. Subcutaneous or intravenous injection of diodrast is quite simple and in many instances satisfactory results are obtained. Retrograde pyelography is restricted almost entirely to females and those cases in which the other two methods are unsuccessful. The so-called characteristic pyelographic changes seen in a Wilms' tumor are: (1) distortion of the renal pelvis and calices, (2) displacement of the renal pelvis upward, downward, or laterally, depending on the position of the tumor within the kidney, and (3) failure of visualization of the kidney pelvis. When no contrast medium can be seen in the pelvis or calices on the affected side, the diagnostician must think of hydronephrosis as well as neoplasm. Aspiration as a diagnostic procedure has been thrown into discard.

The following policy has been adopted for treating these patients. Preoperative irradiation is reserved for those cases in which the tumor is so large that operative removal presents serious technical difficulties. This naturally means that the majority of the patients receive preoperative irradiation, for one of the outstanding features of this tumor is the enormous size to which it grows before giving rise to any symptoms. Postoperative irradiation was formerly employed only in those patients in whom regional metastases were grossly evident at the time of operation or pathologic study of the regional lymph nodes showed metastatic involvement. Now, however, all patients are given postoperative irradiation, and the authors feel that 3 of the 8 living patients very definitely owe their survival to irradiation.

Of the 16 children in this series, 8 are still living for a period ranging from three and one-half to eleven and one-half years since the institution of treatment. One child, considered inoperable because of questionable chest metastases, was treated by x-ray alone. She has survived ten years and today appears well. Twelve of the 16 patients had nephrectomies, and 7 of these children have lived long enough postoperatively to be considered cures by the standards set up by most authors. Two of these patients, at operation, had gross evidence of retroperitoneal extension of the tumor. They were given postoperative irradiation, and the fact that they are still living shows adequately the value of this procedure. With one exception, all of the 5 patients who had nephrectomies and have since died showed evidence of metastases within six months postoperatively. In the one exception three and one-half years intervened before recurrence of the tumor was evident. Operation

was denied 4 of the 16 patients, either because of pulmonary metastases or because they were in such poor condition that they were considered hopeless operative risks. One of these has already been discussed. The other three died within five months from the time they were first seen.

Treatment of Bladder Tumors. Roger W. Barnes, C. LeRoy Turner, and R. Theodore Bergman. California Med. **65:** 95–97, September 1946.

Properly performed endoscopic electrosection and fulguration is an excellent method of treating bladder tumors, and is preferable to suprapubic removal unless the tumor is more than 5 cm. in diameter or is situated in the ventral portion of the dome of the bladder, in which case the open approach is indicated.

A series of 537 cases of bladder tumors treated during the years 1926 to 1945 is reviewed. Of this number, over a third were discarded because of insufficient data or lack of grading as to malignancy. The remaining cases, 349 in number, were divided into two groups: one treated with electrosection and fulguration, the other receiving, in addition to electrosection, radon implantation. Most of the tumors in the latter group were of grade II malignancy or higher. Radon seeds were usually implanted through the cystoscope four weeks after resection and fulguration of the growth.

On an analysis of those cases which were followed until death, it was found that patients with grade II and grade III tumors who were treated with electrosection plus implantation of radon seeds lived longer than those in the group not receiving radiation. The difference is significant, for the average length of life from the onset of symptoms to death in the group in which no radon seeds were implanted was approximately two-thirds of that in the irradiated group. This superiority of the combined treatment is borne out by analyses of the group of patients still alive and of the entire series. It has been the authors' experience that the higher the histologic grade of malignancy the poorer the prognosis. MAURICE D. SACHS, M.D.

Carcinoma of the Penis. Herman Lenowitz and Albert P. Graham. J. Urol. **56:** 458–484, October 1946.

One hundred white patients and 39 Negro patients with carcinoma of the penis were studied at Hines Veterans Hospital from 1931 to 1944. The incidence was found to be 5 1/2 times as high in Negro cancer patients as in white, whereas cutaneous carcinoma in general occurs 7 times as frequently in white patients. Of the treated patients (138) 70 are alive and 68 have died. The disquieting finding in this excellent study is the fact that the average time elapsing from the onset of the lesion until admission to the hospital was twenty-one months. Many patients had had ineffectual treatment or the true nature of the lesion had been overlooked.

The study reveals that circumcision, if done early in life, is probably a good prophylactic measure against penile cancers. It was found that the venereal disease rate in these patients was considerably higher than in the general population, as shown by U. S. Public Health surveys and control studies on other hospital patients. It was felt that irritation, trauma, and chronic inflammation were many times etiologic agents, and case reports are included to illustrate this point. Pathologically the lesion is usually a cutaneous cancer and most frequently it is seen in papillary form. In the order of their frequency of appearance the following sites are listed: (1) frenum and prepuce, (2) glans, and (3) corona. It was deduced that marital status had no effect on the occurrence of cancer of the penis and in no instance did the wife of a patient have carcinoma of the female genital tract.

The usual presenting symptom in these patients is, of course, the presence of a new growth. Other symptoms are pain, a discharge from beneath the prepuce, bleeding, urinary obstruction, increasing phimosis, balanitis, balanoposthitis, urinary fistula, and enlargements in the groin. All too frequently the initial lesion is thought to be venereal both by the patient and the physician and is treated as such.

The place of roentgen therapy at Hines Veterans Hospital is an important one. Radium has not proved to be superior in any way and is not ordinarily used. In lesions 2 cm. or less in diameter, not invading Buck's fascia, the treatment is irradiation alone. An adequate dose (about 5,000 r) is delivered in three weeks or less. In larger lesions and in those invading Buck's fascia, surgery is done and preoperative radiation is given to the primary lesion only, in an effort to reduce its size, reduce infection, and to seal off lymphatic channels; 2,000 to 4,000 r are given. No preoperative therapy is given to the inguinal nodes. Postoperative therapy is given to the node-bearing area when block dissection has been done, and it is felt that this therapy is effective in preventing recurrence. Preoperative therapy to lymph nodes is believed to be ineffective in sterilizing the cancer-bearing nodes and to make subsequent surgery more difficult. Lastly roentgen therapy is used palliatively to decrease tumor mass and to control hemorrhage, pain, and the foul odor incident to this disease. It was observed that patients gained weight and strength and that many months of comfort could be added to life by such palliative therapy. The authors make no effort to list specific technics for each set of conditions, but all forms of therapy from 100 kv. with 1.0 mm. Al filter at 20 cm. distance to 200 kv. with 0.5 mm. Cu filter at 50 cm. distance are used as the condition may require.

Emasculation is not performed unless the scrotum is directly involved by tumor. Bilateral block dissections of the groin are done when the lesion is large and clinically involved nodes are present on one or both sides.

The authors suggest that improvement in end-results might be obtained by reducing the length of the delay period in seeking and obtaining proper treatment for these lesions. JAMES C. KATTERJOHN, M.D.

Nitrogen Mustard Therapy. Use of Methyl-Bis-(Beta-Chloroethyl)amine Hydrochloride and Tris-(Beta-Chloroethyl)amine Hydrochloride for Hodgkin's Disease, Lymphosarcoma, Leukemia, and Certain Allied and Miscellaneous Disorders. Louis S. Goodman, Maxwell M. Wintrobe, William Dameshek, Morton J. Goodman, Alfred Gilman, and Margaret T. McLennan. J. A. M. A. **132:** 126–132, Sept. 21, 1946.

In this preliminary communication, the authors present the clinical results obtained for 67 patients treated intravenously with the nitrogen mustards (halogenated alkyl amine hydrochlorides) for Hodgkin's disease, lymphosarcoma, leukemia, and certain related and miscellaneous diseases. Complete reports including pathologic observations and detailed hematologic data will be published later.

Salutary results were obtained particularly in Hodgkin's disease, lymphosarcoma, and chronic leukemia. Indeed, in the first two disorders dramatic improvement was observed. Some patients fail to benefit from β-chloroethylamine therapy, and the cause of this failure is not known. Varied responses have been observed in acute and subacute leukemias.

In an impressive proportion of terminal and so-called radiation-resistant cases, especially of Hodgkin's disease and lymphosarcoma, the β-chloroethylamines have produced clinical remissions lasting from weeks to months. There is evidence to suggest that responsiveness to radiation therapy may occasionally be restored after a course of nitrogen mustard therapy.

The margin of safety in the use of these chemicals is narrow, necessitating the exercise of considerable caution. Great care must be taken in administration to prevent extravasation of the solution or its contact with skin or mucous membranes. The blood picture must be carefully followed at frequent intervals as a guide to subsequent dosage. Immediate local or systemic side effects are relatively inconsequential and can sometimes be avoided or mitigated by careful technic. More serious late toxic effects are concerned with the blood-forming organs and can be largely avoided by adherence to safe dosage schedules.

Although indications and contraindications for the use of the nitrogen mustards remain to be established definitely, it is felt that these agents are deserving of further clinical trial in Hodgkin's disease, lymphosarcoma, and leukemia. Like radiation, they do not cure but offer only symptomatic palliation.

NON-NEOPLASTIC DISEASE

A Comparison of the Effectiveness of Radiation Therapy and Estrogenic Substance in the Management of Hyperthyroidism. Ernest H. Planck. South. M. J. **39:** 794–799, October 1946.

The author reviews briefly the latest theories and schools of thought on the function of the thyroid gland and the development of hyperthyroidism. Methods of treatment of the latter condition and the recent use of estrogenic substance are presented. The basis for the use of massive doses of estrogenic substance is that it produces a depressant effect upon the anterior pituitary body, thereby reducing the production of thyrotropin and thus, indirectly, improving the condition of hyperthyroidism.

A small series of 16 cases, 8 treated by x-ray and 8 by estrogenic substance, is presented with charts showing the average responses in the two groups. X-ray therapy consisted of 1200–1600 r, at 200 kv.p., given over two areas of the neck. Estrogenic therapy consisted of 5 mg. of diethylstilbestrol given once or twice a week for four weeks, then one dose every two weeks until a total of six months had elapsed. The charts indicate that the estrogenic therapy was more effective. The author also feels that this latter treatment is simpler and less expensive. Two cases are cited in which combined x-ray and estrogenic therapy followed previous thyroidectomies; the estrogenic therapy apparently produced a more decided improvement than the x-ray therapy. Finally a single case is presented in which estrogenic therapy was used preoperatively with good results.

MORRIS IVKER, M.D.

A New Method of Local Treatment of Rheumatoid and Traumatic Affections of the Joints, with Emphasis on a New Approach in the Management of Arthritis and Allied Conditions. Otto C. Kestler. Geriatrics **1:** 150–163, March–April 1946.

This is a report of 65 patients with arthritis who were treated with radon ointment at the Orthopedic Outpatient Department of the New York Polyclinic Medical School and Hospital. Cases of three types were selected and grouped as follows: (1) the so-called chronic rheumatoid group, including rheumatoid arthritis, periarthritis, bursitis, periostitis, and epicondylitis; (2) so-called hypertrophic arthritis or osteoarthritis; (3) post-traumatic conditions, including (*a*) traumatic arthritis, (*b*) post-traumatic painful atrophies of bones and joints, particularly Sudeck's atrophies or cases similar to Sudeck's atrophies, (*c*) stiff joints, post-immobilization in plaster of paris, or postoperative cases. Of the 65 patients, 32 were symptom-free after the treatment with radon ointment; 32 were improved, with decrease of pain; 2 noticed no change. No deleterious effects were experienced.

The radon ointment must be sealed onto the area by an airtight bandage. The strength of the ointment used in the cases reported was 200 electrostatic units per cubic centimeter. The quantity depends upon the size of the skin area to be covered, varying from 5 to 30 c.c. for each treatment. The ointment is squeezed from the tube directly onto the skin and smoothed to a thickness of 1 mm. with a wooden spatula. Several layers of gauze cut to a size a little larger than the area of the ointment are then applied, and this is covered with oiled silk or cellophane and sealed with adhesive tape. Applications are made twice a week, and each bandage is kept on for forty-eight hours. The highest number of treatments given to any patient was fourteen. To avoid discouragement, the physician should prepare the patient for possible recurrences or less than complete recovery. Only regular observation and several courses of treatment will give the patient, not a cure, but permanent relief.

Besides producing physiological changes on the irradiated area, the alpha-ray therapy results in a hyperemia of therapeutic importance. It manifests itself in an erythema, appearing after every application and becoming darker and more pronounced as the use of the radon ointment is continued. The patient should be prepared for this. Sometimes blister formations are observed. In this event, the alpha-ray treatments should be interrupted and a reasonable period allowed to elapse before treatment is resumed. These blisters are extremely superficial, similar to those produced by light sunburn, and will disappear with the usual treatment.

Chromoblastomycosis: Report of Two New Cases Observed in the Isthmus of Panama. Carlos Calero. Arch. Dermat. & Syph. **54:** 265–277, September 1946.

Two new cases of chromoblastomycosis are described by the author, making a total of 154 cases thus far recorded. Both patients were white males. The first showed multiple large crusted verrucae of the foot and leg which had been present for eight years. The second had similar lesions on the hand which had been present for two and one-half years. The diagnosis was made by culturing the scabs on Sabouraud's medium and studying the fungi microscopically. The lesions on the

leg were treated solely by roentgen rays. From Dec. 22, 1944, to April 4, 1945, a total of 11,700 r was given to the areas. A filter of 2 mm. of copper and 1 mm. of aluminum was used, but the voltage and distance factors are not given.

The lesions on the hand were treated by electrocautery and ten irradiations totaling 1,000 r were given to the area. The author is not sure that a full cure was obtained in the case receiving x-ray therapy (the patient was not seen following discharge from the hospital), but he believes that the case treated surgically was completely cured.

JOSEPH T. DANZER, M.D.

DOSAGE

Dose Measurements with Radium Beta-Ray Applicators. G. J. Neary. Brit. J. Radiol. **19:** 357–367, September 1946.

With the development of the betatron, it seems likely that therapy with fast electrons will become available, so that the study of beta-ray applicators is in order. This type of applicator, designed for the therapeutic utilization of the primary beta radiation of radium, has not been much used in recent years and consequently has received little physical study. The old belief that beta rays were caustic arose because unscreened plaques were used for their gamma-ray effect, with the result that large beta-ray doses were delivered superficially. The caustic effect actually is due to this excessive dosage rather than to any qualitative effect of the rays.

The maximum effective range of beta radiation is about 1.5 cm. in material of unit density. New plaques reach equilibrium in about five weeks, but the output may rise slowly for years.

Since gamma radiation produces ionization by the intermediate agency of beta particles, it seems reasonable to measure primary beta radiation like gamma radiation, by air ionization corrected to standard conditions of temperature and pressure. The quantity thus determined, expressed in e.s.u. per c.c., is termed the dose of beta radiation in roentgens. Because the dose rates of the applicators are high and the decrease with distance is great, very shallow chambers are necessary for measurement. As beta rays ionize air directly, there is no question of wall effect. It is only necessary that the walls should not absorb an appreciable amount of the radiation.

Under the conditions of measurement, the gamma-ray component is measured also. However, the gamma-ray effect near the surface is only a small fraction of the beta-ray component. At greater depths, where the relative importance of gamma rays enters into consideration, due to the absorption of beta rays by the additional material around the chamber, the gamma-ray component more nearly governs the dose rate.

The thickness of the ionization chamber affects measurements at the upper surface of the phantom. For distances closer than 0.75 mm. the dose is obtained by extrapolation.

Applicators having 5 mg. of radium element per sq. cm. usually show a surface dose rate of the order of 5,000 r/hr. There is little effect of size, for the oblique filtration is so marked that it cuts out practically all the radiation except that coming from a small area near the point being measured. A concomitant effect is that the dose rate is practically uniform over most of the area of the applicator provided the radium loading is uniform. For the same reason, depth doses do not vary as much as would be expected with the size of the applicator. For example, a comparison at the depth of 1 mm. shows only 15 per cent greater depth dose from an applicator with a diameter of 2 cm. than from one of 1 cm. diameter.

Surface dose rates varied irregularly with similar applicators. This variation parallels the beta-gamma ray ratio, which was found to be about 25 to 1 for high-output applicators. High-output applicators were found to have low inherent filtration. Relatively more "soft" radiation was found from the high-output applicators and there was progressive hardening as the inherent filtration was increased. These differences were found to be due chiefly to differences in the composition of the radium salt mixture. The type of backing and the degree of equilibrium reached by radium E will also affect the strength. Thus for various reasons it is not sufficient with beta-ray applicators to rely on the radium content and distribution, but each applicator must be measured.

The most striking observation in depth-dose measurement is the rapid fall with increasing depth, namely to about 50 per cent at 1 mm. There is little difference in depth percentages with different filters, except that 0.1 mm. of lead approximately doubles the depth dose at 4 mm., but at the expense of a fourfold reduction in the surface dose. Absorption was shown to have much more effect on the fall in depth dose than distance. Back-scatter appears to have only a small influence, probably less than 10 per cent.

Studies were made on absorption and reflection effects of beta radiation by measurements with radium (B plus C) and radium E sources. The specific beta-ray dose rate at zero filtration is 1,180 r/mc.hr. for radium (B plus C) and 525 r/mc.hr. for radium E, and 1,710 r/mc.hr. for radium in final equilibrium, excluding the soft radiation from radium D.

SYDNEY J. HAWLEY, M.D.

Dose Measurement in Beta-Ray Therapy. G. W. Bloomfield and F. W. Spiers. Brit. J. Radiol. **19:** 349–356, September 1946.

Studies were made of the dose from beta-ray plaques by means of a small condenser ionization chamber and wax and water phantoms. The unit of dosage used was e.s.u./c.c., called for the authors' purposes a "roentgen." Two plaques of somewhat different construction were investigated. A comparison of the measurements obtained with measurements made by Neary with a different type of apparatus shows good agreement at distances of 1 mm. or more from the plaque. Nearer the plaque surface, the design of the ionization chamber and the position of the plaque affect slightly the accuracy of the measurements.

A study was also made of the dose delivered when a reflector was used to cover a greater area, after the manner of a beta-ray "bomb." Observations with plane and elliptical reflectors showed that the increase in dose was less than had previously been reported. The use of reflectors therefore seems to be more of a convenience than an economy. Depth dose measurements in water phantoms also failed to show any significant difference between contact positions and with reflectors. The depth dose was found to drop to 50 per cent at 1.5 mm. and to 20 per cent at 3.3 mm.

In practice it was found that superficial rodent ulcers were cured by a beta-ray plaque with doses of 6,000 to

7,000 r at the surface. The dose at 0.25 cm. was approximately 2,000 r, and at 0.5 cm. 600 r, under these conditions. In order to assess this dosage, minimal erythemas on 1 sq. cm. of skin were compared with that produced by x-rays at 180 kv.p. F.S.D. 40 cm., h.v.l. 0.9 mm. Cu. It was found that 750 r of beta-rays produced erythemas equivalent to those produced by 700 r, of x-rays.

The authors conclude that radiations from beta-ray plaques can be satisfactorily measured by ionization methods. Such plaques give a stable output over a period of years and may be used successfully for superficial lesions where no more than 30 per cent depth dose is needed at 0.25 cm. Such lesions are shallow rodent ulcers, port wine marks, and hyperkeratoses. In terms of depth dose, beta radiation corresponds to "grenz" rays generated at 25 kv., but its energies and ranges are equivalent to those of secondary electrons released by homogeneous x-rays of some 1.6 MV energy.

SYDNEY J. HAWLEY, M.D.

New Units for the Measurement of Radioactivity. E. U. Condon and L. F. Curtiss. Brit. J. Radiol. **19:** 368, September 1946.

As the curie is defined as that amount of radon in equilibrium with one gram of radium, it should be used only to represent the disintegration in the radium family. A new and more suitable unit is proposed, the "rutherford," abbreviated "rd," which may be used for any radioactive disintegration. The rutherford is 10^6 disintegrations per second. A micro-rutherford thus would be one disintegration per second. This is readily remembered, easily measured, and is of sufficient difference in size from the curie so that no confusion would result.

For the measurement of gamma-ray sources the roentgen-per-hour at one meter is suggested. This would be abbreviated rhm and pronounced "rum." The gamma-ray strength of any source of 1 rhm is 1.18 times that of 1 curie.

SYDNEY J. HAWLEY, M.D.

EFFECTS OF RADIATION

Pathologic Effects of an Instantaneous Dose of Radiation. Shields Warren. Cancer Research **6:** 449–453, September 1946.

The distinctive feature of the atomic bomb is the large amount of radiant energy that it produces. While this energy covers a wide range of the electromagnetic spectrum, its chief physiologic and pathologic results may be divided into two groups: first, the effects of heat (primary thermal injury of the flash-burn type and secondary thermal injuries due to induced fires); second, the effects of short-wave radiation and neutrons, paralleling closely the effects made familiar by experimental studies of the biologic effects of x-rays. Combined with and modifying and obscuring these injuries are the more usual effects of the conventional type of bomb, chief among which are injuries due to flying debris or impact against fixed structures.

In the studies of the atomic bomb effects at Nagasaki and Hiroshima, carried out under the direction of the Naval Medical Research Institute, particular attention was given to the injuries due to radiation. The immediate effects were manifested as weakness, malaise, fever, and often death, and appeared usually within forty-eight hours, while the delayed effects manifested themselves in a variety of ways.

Unfortunately, the disorganization of the Japanese was so great that no adequate material exists to determine the exact nature of immediate effects. The present study, dealing with the later effects, is based on a casualty survey of 13,000 survivors.

There were three chief, somewhat overlapping, symptom complexes due to damage to the hematopoietic tissue. The first was the leukopenic group, in which infection, particularly Ludwig's angina, was the outstanding manifestation. The great bulk of leukopenic deaths occurred during the first three weeks following the bombing. According to the studies of the Japanese investigators, the leukocytes in the circulating blood were destroyed at the same time the hematopoietic system was damaged, so that white blood cell counts as low as 200 per cu. mm. were found in the first few days.

From three to five weeks after the bombing a considerable number of hemorrhagic deaths occurred, associated with thrombocytopenia induced by radiation damage to the megakaryocytes of the bone marrow. It is suggested that the blood platelets in the circulation were not destroyed by the radiation and that only as a low point was reached as a result of deficiency in blood did hemorrhagic manifestation occur.

Those with serious bone marrow damage who weathered the first few weeks showed later anemic manifestations with red blood cell counts in some instances dropping to one million or below.

As would be expected, the gonadal effect was much more prominent in case of the testis than of the ovary. Ova were present in the ovaries in many cases; only occasionally in women of the child-bearing age did atrophy occur. However, it was relatively unusual to find a recent corpus hemorrhagicum or corpus luteum. In the testis, on the other hand, in men who had been exposed to appreciable amounts of radiation, atrophy of the germinal epithelium was striking.

No deleterious effects from residual radioactivity could be found in persons who had entered the bombed areas soon after the explosion and remained there.

Radiation Effects of the Atomic Bomb Among the Natives of Nagasaki, Kyushu. James S. P. Beck and William A. Meissner. Am. J. Clin. Path. **16:** 585–592 September 1946.

Some of the radiation effects of atomic bombing among the natives of Nagasaki are reported. Among 20 patients whose blood or bone marrow was studied, there were anemia, neutropenia, and thrombocytopenia, or depression of the marrow. In 7 postmortem examinations, there was confirmatory evidence of damage to the bone marrow. Evidence of recovery of bone marrow was observed both clinically and at necropsy. Histologic evidence of lipoid depletion of cells of the adrenal cortex was found. Aspermatogenesis was noted in some instances. The mortality rate could have been lowered by adequate medical care.

Radium Dial Painting—Medical Status of Workers. Irving R. Tabershaw. J. Indust. Hyg. & Toxicol. **28:** 212–216, September 1946.

A survey was made of 52 radium dial painters employed a minimum of eighteen months. A history

was taken of each individual; the physical and dental condition, blood counts, and nutritional status were determined, and these findings were correlated with breath-radon analyses. Results of this survey again emphasize that careful attention to the hazards of radium in dial painting is necessary and that an educational campaign regarding working habits, personal hygiene, and attention to the teeth and blood must be stressed. No deleterious effects may be expected within a year and a half to four years of employment when the radium content of the body is kept below 0.1 microgram. Reliance on medical examination is not an adequate safeguard; analysis of breath radon is practical and reliable.

EXPERIMENTAL STUDIES

Experimental Radiotherapeutics. Joseph S. Mitchell. Schweiz. med. Wchnschr. **76:** 883–889, Sept. 16, 1946.

This article is an abstract of the recent advances in research on the mechanisms of radiotherapeutic effects, presented at the British-Swiss Medical Conference at Basle. These advances are ascribed to improved methods of employing radioactive tracers and to advances in cytology, cytochemistry, genetics, and nuclear physics. The author considers the following of special interest: the inhibition of thymonucleic acid synthesis by radiations, the significance of chromosome breakage, the dependence of biologic efficiency on speeific ionization, the production of artificial gamma ray sources for therapy, and the possible applications of radioactive isotopes, high-energy gamma radiations, and fast neutrons. The article is so condensed as to be intelligible only with difficulty, but has a bibliography to which liberal reference is made for those who wish fuller discussion. LEWIS G. JACOBS, M.D.

Influence of Wave-Lengths on Certain Lesions Produced by the Irradiation of Mice. A. Lacassagne. Proc. Roy. Soc. Med. **39:** 605–612, August 1946.

This author describes the results of treatment of mice with K radiation of molybdenum, ultraviolet rays, and L radiation of silver. The objective in using the K radiation of molybdenum was the production of complete sterilization of female mice two months old. These mice were treated with unfiltered rays with an effective wave length of 0.95 Å., at 35 kv.p., 15 ma., and focal skin distance of 12 cm. The dosage rate was 3,000 r per minute. Two areas 1 cm. square on the dorsal surface of each mouse, centered as close as possible over the ovaries, were treated. Four groups of mice were used, receiving 3,000, 4,500, 6,000 and 9,000 r, respectively. Two mice of the 6,000 r group and all of the 9,000 r group died less than nine weeks later.

The only cutaneous reaction which followed these dosages was the loss of hair over the exposed areas occurring about the twentieth day, regardless of the dose. In no case was there any sign of ulceration. A sparse regrowth of hair occurred in the animals receiving the smaller doses. In a few, there was slight sclerosis of the fatty tissue and some atrophy of the cutaneous muscle. In only a small proportion was complete sterilization accomplished. In only 3 of 11 mice that survived was there total atrophy of both ovaries. All of these had received 4,500 r or more. In most cases it was impossible, because of the smallness of the test object, to exactly center both ovaries, and unilateral ovarian atrophy resulted. Histologic studies showed almost complete destruction of the follicles, and the parenchyma was riddled with cavities, cystic in nature.

In addition to the changes in the ovaries, some of these mice showed extreme atrophy of the lower pole of the kidney, undoubtedly due to the radiation. Histologic study of these affected kidneys showed most of the destructive effect to be in convoluted tubules. The glomeruli as a rule appeared intact and seemed to be capable of functioning, but since the tubules were destroyed and there was no place for the infiltrating liquid to escape, it distended the capsules. The irradiated area therefore assumed somewhat the appearance of a polycystic kidney. There was thus demonstrated a definite difference between the extreme sensitivity of the epithelial cells and the apparent integrity of the vascular formations.

Ultraviolet rays, in large dosage (1,500 finsens) produced a necrotic dermatitis with edema beyond the irradiation area within a few hours. Following this was an intense erythema lasting five to six days. Histologic examination of the skin showed rapid local necrosis involving every variety of cell. The destruction is not deep-seated, however, and the repair process is rapid and early.

The L radiation of silver was generated by a tube operated at 4.5 kv.p. and 15 ma., with a thin window of aluminum. A dose of 500 ergs per square millimeter produced a lesion macroscopically comparable to that obtained with 1,500 f of ultraviolet rays. This was given to 11 young mice. Reactions were less rapid and severe than those produced by ultraviolet rays. There was a pronounced erythema on the third day followed by pigmentation. On the eighth day there was severe desquamation followed by superficial ulceration and a scab on about the twelfth day. This separated on the sixteenth day, exposing a red, smooth and hairless epidermis. Regrowth of hair began on the thirtieth day.

Histologic study showed cellular changes which started very early but affected only certain elements sensitive to radiation. This selective action was confined to the invaginations of the epidermis which were to constitute the hair follicles. Many of these showed signs of advanced degeneration, whereas the epidermis showed no more than a simple cellular swelling and the dermis no reaction. Cornification of the whole epidermis and degeneration of the follicular buds was advanced on the fifth day. On the ninth day the degeneration of the whole epidermis was complete. By the eleventh day a smooth thin epidermis had formed under the skin. This selective action of the rays on the cells of the germinative process agrees with previous accounts of epidermitis due to irradiation but differs markedly from the diffuse necrosis produced by ultraviolet rays.

In conclusion, this author has shown that there is a distinct difference in the cutaneous response to radiations of radically different wave lengths when a comparable quantity of each of the radiations is used.

BERNARD S. KALAYJIAN, M.D.

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